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(54) Title: 1,2,3,4-TETRAHYDROISOQUINOLINES DERIVATIVES AS UROTENSIN II RECEPTOR ANTAGONISTS

(57) Abstract: The invention relates to novel 1,2,3,4-tetrahydroisoquinoline derivatives of formula (I) and related compounds and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as neurohormonal antagonists especially urotensin II antagonists.

1,2,3,4-TETRAHYDROISOQUINOLINES DERIVATIVES AS UROTENSIN II RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

The present invention relates to novel 1,2,3,4-tetrahydroisoquinoline derivatives of the general formula 1 and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of the general formula 1 and especially their use as neurohormonal antagonists.

BACKGROUND OF THE INVENTION

Urotensin II is a cyclic 11-amino acid peptide that has some sequence similarity to, but is not homologous with, somatostatin-14. Urotensin II was first isolated and sequenced from fish spinal cord (Bern HA, Pearson D, Larson BA, Nishioka RS. Neurohormones from fish tails: the caudal neurosecretory system. I. "Urophysiology" and the caudal neurosecretory system of fishes. Recent Prog. Horm. Res. (1985) 41, 533-552), and has since been found in a wide variety of vertebrate and invertebrate species. Human urotensin II is synthesized in a prepro-form from a single gene located at chromosome 1p36.21, and two cDNA splice variants which differ in their putative signal peptide sequence have been isolated from human colon tumor and human placenta (GenBank Accession Nr. O95399). The putative prohormone convertase dibasic cleavage site is strictly conserved across species. The mature 11-amino acid peptide contains a C-terminal disulfide-bridged 6-amino acid loop which is also strictly conserved, while the N-terminal portion of the mature cyclic peptide can vary considerably across species.

Urotensin II exerts potent and complex hemodynamic actions in mammals (Douglas SA, Sulpizio AC, Piercy V, Sarau HM, Ames RS, Aiyar NV, Ohlstein EH, Willette RN. "Differential vasoconstrictor activity of human urotensin-II in

vascular tissue isolated from the rat, mouse, dog, pig, marmoset and cynomolgus monkey." Br. J. Pharmacol. (2000) 131, 1262-1274. Douglas, SA, Ashton DJ, Sauermelch CF, Coatney RW, Ohlstein DH, Ruffolo MR, Ohlstein EH, Aiyar NV, Willette R "Human Urotensin-II is a potent vasoactive peptide: pharmacological characterization in the rat, mouse, dog and primate." J. Cardiovasc. Pharmacol. (2000) 36, Suppl 1:S163-6). The peptide effectively constricts isolated mammalian arteries. The potency of vasoconstriction is an order of magnitude greater than that of endothelin-1. These effects appear to be mediated at least in part via the actions of urotensin II on a G-protein coupled receptor named GPR-14 or SENR (Ames RS, et al. "Human urotensin-II is a potent vasoconstrictor and agonist for the orphan receptor GPR14." Nature. (1999) 401, 282-6. Mori M, Sugo T, Abe M, Shimomura Y, Kurihara M, Kitada C, Kikuchi K, Shintani Y, Kurokawa T, Onda H, Nishimura O, Fujino M. "Urotensin II is the endogenous ligand of a G-protein-coupled orphan receptor, SENR (GPR14)" Biochem. Biophys. Res. Commun. (1999) 265,123-9. Liu Q, Pong SS, Zeng Z, et al. „Identification of urotensin II as the endogenous ligand for the orphan G-protein-coupled receptor GPR14" Biochem. Biophys. Res. Commun. (1999) 266, 174-178.) GPR14 is expressed in arterial (but not venous) smooth muscle cells, on atrial and ventricular cardiac myocytes, in pancreas, kidney, and in the brain.

In addition to its vasoconstrictive actions, urotensin II potently affects atrial and ventricular muscle contraction (Russell FD, Molenaar P, and O'Brien DM "Cardiostimulant effects of urotensin-II in human heart in vitro". Br J Pharmacol (2001) 132, 5-9).

Urotensin II stimulates cellular proliferation, migration and collagen synthesis in cardiac fibroblasts (Tzandis A, et al., "Urotensin II stimulates collagen synthesis by cardiac fibroblasts and hypertrophic signaling cardiomyocytes via G(alpha)q- and Ras-dependent pathways". J. Am. Coll. Cardiol. (2001) 37, 164A.) and in neonatal myocytes (Zou Y, Nagai R, and Yamazaki T, "Urotensin II induces hypertrophic responses in cultured cardiomyocytes from neonatal rats". FEBS Lett (2001) 508, 57-60). Urotensin II is produced by cancer cell lines and its receptor is also expressed in these cells. (Takahashi K, et al., "Expression of urotensin II and urotensin II receptor

mRNAs in various human tumor cell lines and secretion of urotensin II-like immunoreactivity by SW-13 adrenocortical carcinoma cells". Peptides (2001) 22, 1175-9).

Urotensin II modulates glucose-stimulated pancreatic release of insulin (Silvestre RA, et al., "Inhibition of insulin release by urotensin II--a study on the perfused rat pancreas". Horm Metab Res (2001) 33, 379-81).

Elevated circulating levels of urotensin II are detected in humans susceptible to high-altitude pulmonary edema, and in patients awaiting kidney transplantation (Totsune K, et al., "Role of urotensin II in patients on dialysis". Lancet (2001) 358, 810-1).

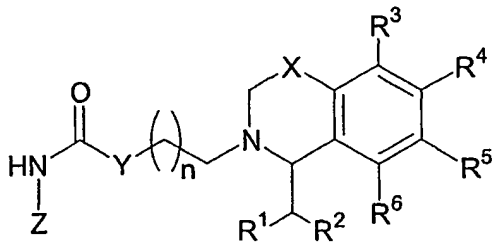
Urotensin II and its receptor are found in spinal cord and brain tissue, and intracerebroventricular infusion of urotensin II into mice induces behavioral changes (Gartlon J, et al., "Central effects of urotensin-II following ICV administration in rats". Psychopharmacology (Berlin) (2001) 155, 426-33).

Substances with the ability to block the actions of urotensin II are accordingly expected to prove useful in the treatment of various diseases. WO-2001/45694 discloses certain sulfonamides as urotensin II receptor antagonists, and their use to treat diseases associated with a urotensin II imbalance. WO-2001/45700 discloses certain pyrrolidines as urotensin II receptor antagonists and their use to treat diseases associated with a urotensin II imbalance. WO-2001/45711 discloses certain pyrrolyl and pyridyl derivatives as urotensin II receptor antagonists and their use to treat diseases associated with a urotensin II imbalance. WO-2002/00606 discloses certain biphenyl compounds useful as urotensin II receptor antagonists, and WO-2002/02530 also discloses certain compounds useful as urotensin II receptor antagonists.

The present invention comprises 1,2,3,4-tetrahydroisoquinoline derivatives which are novel compositions of matter and which are urotensin II receptor antagonists. EP 428434 discloses certain alkylureidopyridines as neurokinin and substance P antagonists. WO-99/21835 discloses certain ureidoquinolines as H+-ATPase and bone resorption inhibitors. WO-01/009088 discloses certain substituted heteroarylureas as inhibitors of the CCR-3 receptor.

DESCRIPTION OF THE INVENTION

The present invention relates to compounds of the general formula 1,



General Formula 1

wherein

X represents $-CH_2-$, $-CH_2CH_2-$, $-C(CH_3)_2-$;

Y represents oxygen, NH;

n represents the numbers 1 or 2;

Z represents quinolin-4-yl which may be mono-substituted with lower alkyl in the positions 2, 6, or 8, or di-substituted with lower alkyl in the positions 2,6 or 2,8; [1,8]naphthyridin-4-yl which may be substituted in position 7 with lower alkyl; pyridin-4-yl which may be substituted in position 2 with R^7R^8N- and additionally in position 6 with hydrogen or lower alkyl;

R^1 represents naphthalen-1-yl; naphthalen-2-yl; benzo[1,3]dioxol-5-yl; benzyl, or mono-, di-, or tri-substituted benzyl substituted in the phenyl ring independently with lower alkyl, lower alkyloxy, trifluoromethyl, halogen, cyano; phenyl, or mono- , di- or tri-substituted phenyl, substituted independently with lower alkyl, lower alkyloxy, trifluoromethyl, halogen, cyano;

R^2 represents hydrogen, lower alkyl, aryl or forms with R^1 a styryl group of E or Z geometry, whereby the phenyl ring in the styryl group may be mono-, di- or tri-substituted phenyl, substituted independently with lower alkyl, lower alkyloxy, trifluoromethyl, halogen, cyano;

R^3, R^4, R^5 and R^6 independently represent hydrogen, cyano, hydroxy, lower alkyloxy, aralkyloxy, lower alkenyloxy, and R^5 additionally represents R^7R^8NCO;

R^4 and R^5 together may form with the phenyl ring a five- or a six-membered ring containing one or two oxygen atoms;

R^7 and R^8 independently represent hydrogen, lower alkyl, aryl, aralkyl, or together with the N form a pyrrolidine, piperidine, or morpholine ring;

and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, and mixtures of diastereomeric racemates; as well as their pharmaceutically acceptable salts, solvent complexes, and morphological forms.

In the definitions of the general formula 1 the expression 'lower alkyl' means straight or branched chain groups with one to seven carbon atoms, preferably 1 to 4 carbon atoms; or cyclic alkyl groups with three to six carbon atoms. Preferred examples of lower alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

The expression 'lower alkyloxy' means a group of the formula lower alkyl-O- in which the term 'lower alkyl' has the meaning previously given. Preferred examples of lower alkyloxy groups are methoxy, ethoxy, propoxy, iso-propoxy, butoxy, iso-butoxy, sec-butoxy, tert-butoxy, cyclopentyloxy, and cyclohexyloxy.

The expression 'lower alkenyloxy' means a group of the formula lower alkenyl-O- in which the term 'lower alkenyl' means a straight-chain or branched-chain alkenyl group with 2 to 5 carbon atoms. Preferred examples of lower alkenyloxy groups are allyloxy or propenyloxy.

The expression 'aryl' means a phenyl or naphthyl group which optionally carries one or more substituents, preferably one or two substituents, each independently selected from cyano, halogen, lower alkyl, lower alkenyl, lower alkyloxy, lower alkenyloxy, trifluoromethyl, trifluoromethoxy, amino, carboxy and the like. Preferred examples of aryl groups are phenyl, 4-methylphenyl, 4-methoxyphenyl, 4-cyanophenyl, 4-chlorophenyl, 4-fluorophenyl, 2-methylphenyl, 2-chlorophenyl, 2-fluorophenyl, 2-methoxyphenyl, naphthalen-1-yl and naphthalen-2-yl.

The expression 'aralkyl' means a lower alkyl group as previously defined in which one hydrogen atom has been replaced by an aryl group as previously defined. Preferred examples of aralkyl groups are benzyl and benzyl substituted in the phenyl ring with hydroxy, lower alkyl, lower alkyloxy or halogen.

The expression 'aralkyloxy' means a group of the formula aralkyl-O- in which the term 'aralkyl' has the meaning previously given. Preferred examples of aralkyloxy are benzyloxy and phenethyloxy.

The present invention encompasses pharmaceutically acceptable salts of compounds of the general formula 1. This encompasses either salts with inorganic acids or organic acids like hydrohalogenic acids, e.g. hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, methylsulfonic acid, p- tolylsulfonic acid and the like or in case the compound of formula 1 is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium, potassium, or calcium salts, etc.

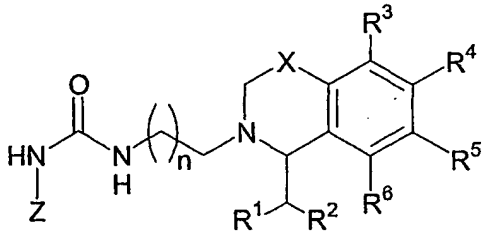
The present invention encompasses different solvation complexes of compounds of general formula 1. The solvation can be effected in the course of the manufacturing process or can take place separately, e.g. as a consequence of hygroscopic properties of an initially anhydrous compound of general formula 1.

The present invention further encompasses different morphological forms, e.g. crystalline forms, of compounds of general formula 1 and their salts and solvation complexes. Particular heteromorphs may exhibit different dissolution properties, stability profiles, and the like, and are all included in the scope of the present invention.

The compounds of the general formula 1 might have one or more asymmetric carbon atoms and may be prepared in form of optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, and mixtures of diastereomeric racemates. The present invention encompasses all these forms. They are prepared by stereoselective synthesis, or

by separation of mixtures in a manner known per se, i.e. by column chromatography, thin layer chromatography, HPLC, crystallization, etc.

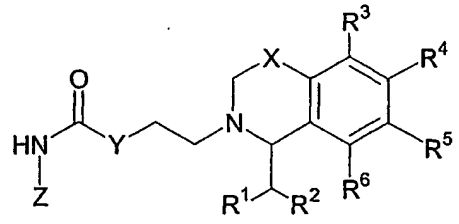
Preferred compounds of general formula 1 are the compounds of general formula 2,



General Formula 2

wherein R^1, R^2, R^3, R^4, R^5, R^6, X, Z, and n have the meaning given in general formula 1 above.

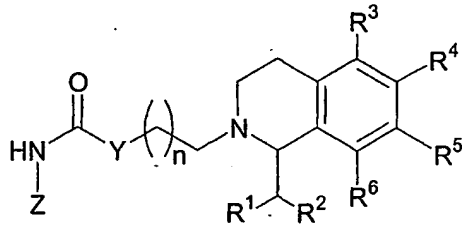
Another group of preferred compounds of general formula 1 are the compounds of general formula 3,



General Formula 3

wherein R^1, R^2, R^3, R^4, R^5, R^6, X, Y, and Z have the meaning given in general formula 1 above.

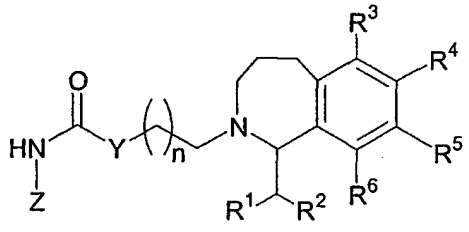
Another group of preferred compounds of general formula 1 are the compounds of general formula 4,



General Formula 4

wherein R^1, R^2, R^3, R^4, R^5, R^6, Y, Z, and n have the meaning given in general formula 1 above.

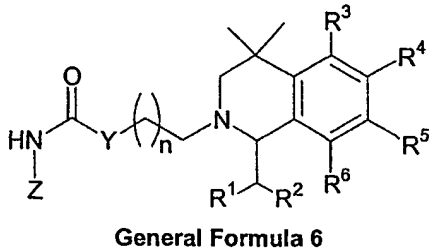
Another group of preferred compounds of general formula 1 are the compounds of general formula 5,



General Formula 5

wherein R^1, R^2, R^3, R^4, R^5, R^6, Y, Z, and n have the meaning given in general formula 1 above.

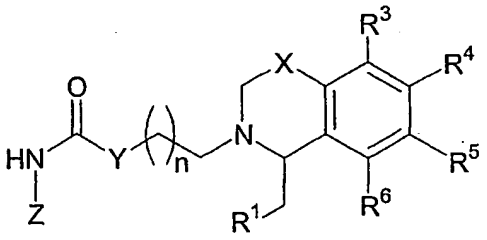
Another group of preferred compounds of general formula 1 are the compounds of general formula 6,



General Formula 6

wherein R^1, R^2, R^3, R^4, R^5, R^6, Y, Z, and n have the meaning given in general formula 1 above.

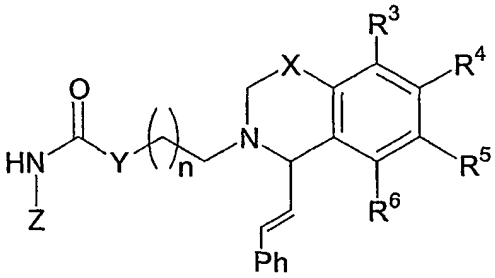
Another group of preferred compounds of general formula 1 are the compounds of general formula 7,



General Formula 7

wherein R^1, R^3, R^4, R^5, R^6, X, Y, Z, and n have the meaning given in general formula 1 above.

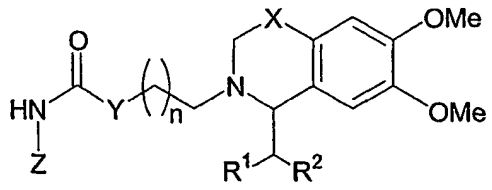
Another group of preferred compounds of general formula 1 are the compounds of general formula 8,



General Formula 8

wherein Ph is phenyl; mono-, di- or tri-substituted phenyl, substituted independently with hydrogen, lower alkyl, lower alkyloxy, trifluoromethyl, halogen, or cyano; and R^3, R^4, R^5, R^6, X, Y, Z, and n have the meaning given in general formula 1 above.

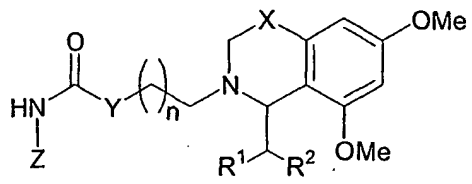
Another group of preferred compounds of general formula 1 are the compounds of general formula 9,



General Formula 9

wherein R^1, R^2, X, Y, Z, and n have the meaning given in general formula 1 above.

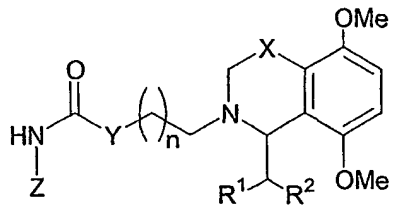
Another group of preferred compounds of general formula 1 are the compounds of general formula 10,



General Formula 10

wherein R^1, R^2, X, Y, Z, and n have the meaning given in general formula 1 above.

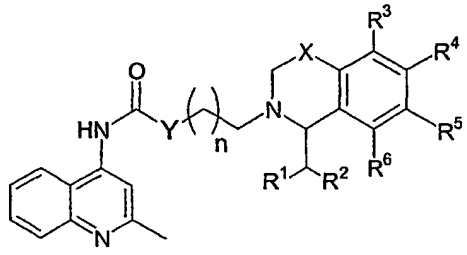
Another group of preferred compounds of general formula 1 are the compounds of general formula 11,



General Formula 11

wherein R^1, R^2, X, Y, Z, and n have the meaning given in general formula 1 above.

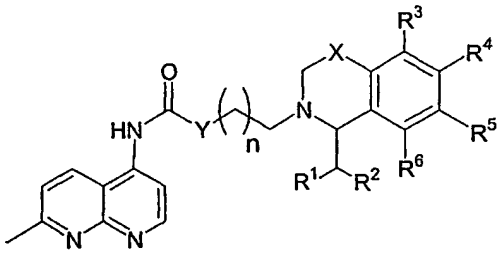
Another group of preferred compounds of general formula 1 are the compounds of general formula 12,



General Formula 12

wherein R^1, R^2, R^3, R^4, R^5, R^6, X, Y, and n have the meaning given in general formula 1.

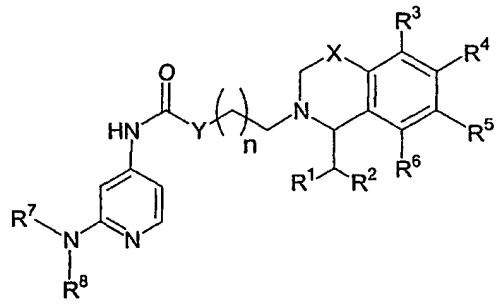
Another group of preferred compounds of general formula 1 are the compounds of general formula 13,



General Formula 13

wherein R^1, R^2, R^3, R^4, R^5, R^6, X, Y, and n have the meaning given in general formula 1.

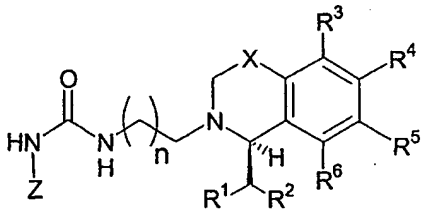
Another group of preferred compounds of general formula 1 are the compounds of general formula 14,



General Formula 14

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X, Y, and n have the meaning given in general formula 1.

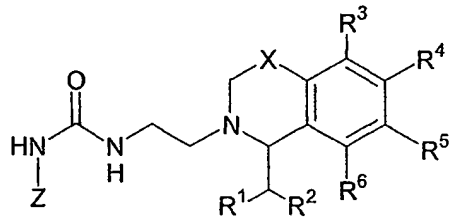
Another group of preferred compounds of general formula 1 are the compounds of general formula 15,



General Formula 15

wherein the 1 position of the 1,2,3,4-tetrahydroisoquinoline ring system has the R absolute stereochemical configuration, and R^1, R^2, R^3, R^4, R^5, R^6, X, Z, and n have the meaning given in general formula 1.

Another group of preferred compounds of general formula 1 are the compounds of general formula 16,



General Formula 16

wherein R^3, R^4, R^5, and R^6 are independently hydrogen or lower alkyloxy; and R^1, R^2, and Z have the meaning given in general formula 1 above.

Examples of particularly preferred compounds of general formula 1 are:

1-{2-[1-(4-Fluoro-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[1-(3,4-Difluoro-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[1-(3-Fluoro-4-methoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[1-(3,4-Difluoro-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(3-Fluoro-4-methoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(4-Fluoro-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-(2-{1-[2-(4-Fluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(2,4-Difluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(2,4-Difluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-quinolin-4-yl-urea

1-(2-{1-[2-(3,4-Difluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(3,4-Difluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-quinolin-4-yl-urea

1-(2-{1-[2-(4-Fluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-quinolin-4-yl-urea

1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[(*E*)-2-(2,4-Difluoro-phenyl)-vinyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[(*E*)-2-(2,5-Difluoro-phenyl)-vinyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(2,3-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(2,4-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(2,5-Bis-trifluoromethyl-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(2,5-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(3,4-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(3,4-Dimethoxy-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(4-Fluoro-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{6,7-Dimethoxy-1-[2-(2-methoxy-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{6,7-Dimethoxy-1-[2-(3-methoxy-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{6,7-Dimethoxy-1-[2-(4-methoxy-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{6,7-Dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-[2-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea

1-[2-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea

1-[2-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea

1-[3-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-propyl]-3-(2-methyl-quinolin-4-yl)-urea

1-[3-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-propyl]-3-quinolin-4-yl-urea

1-[2-(1-Benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea

1-[2-(1-Benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea

1-[2-(1-Benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea

1-[2-(1-Benzyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea

1-[2-(1-Benzyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea

1-[2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea

1-[2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea

1-[2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea

1-[2-(1-Benzyl-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea

1-[2-(1-Benzyl-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea

1-[2-(6,7-Dimethoxy-1-naphthalen-2-ylmethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea

1-[2-(6,7-Dimethoxy-1-naphthalen-2-ylmethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea

1-[2-(6,7-Dimethoxy-1-phenoxymethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea

1-[3-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-propyl]-3-(2-methyl-quinolin-4-yl)-urea

1-[3-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-propyl]-3-quinolin-4-yl-urea

1-{2-[1-(2,5-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[1-(2,5-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(2,6-Dichloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[1-(3,4-Difluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[1-(3,4-Difluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(5,6,7,8-tetrahydro-quinolin-4-yl)-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(3-Fluoro-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[1-(3-Fluoro-5-trifluoromethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[1-(4-Chloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[1-(4-Chloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[6,7-Dimethoxy-1-(2,3,4-trimethoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[6,7-Dimethoxy-1-(2,3,4-trimethoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[6,7-Dimethoxy-1-(3,4,5-trimethoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[6,7-Dimethoxy-1-(3,4,5-trimethoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[6,7-Dimethoxy-1-(3,4,5-trimethoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[6,7-Dimethoxy-1-(3-methoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[6,7-Dimethoxy-1-(3-methoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[6,7-Dimethoxy-1-(4-methoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[6,7-Dimethoxy-1-(4-methoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{3-[1-(3,4-Difluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl}-3-quinolin-4-yl-urea

1-{3-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{3-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl}-3-quinolin-4-yl-urea

1-{3-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{3-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl}-3-quinolin-4-yl-urea

1-{3-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl}-3-quinolin-4-yl-urea

1-{2-[5-(3,4-Dimethoxy-benzyl)-7,8-dihydro-5*H*-[1,3]dioxolo[4,5-g]isoquinolin-6-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[5-(3,4-Dimethoxy-benzyl)-7,8-dihydro-5*H*-[1,3]dioxolo[4,5-g]isoquinolin-6-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[6-(3,4-Dimethoxy-benzyl)-2,3,8,9-tetrahydro-6*H*-[1,4]dioxino[2,3-g]isoquinolin-7-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[6-(3,4-Dimethoxy-benzyl)-2,3,8,9-tetrahydro-6*H*-[1,4]dioxino[2,3-g]isoquinolin-7-yl]-ethyl}-3-quinolin-4-yl-urea

1-[2-(1-Benzhydryl-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea

1-[2-(1-Benzhydryl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea

1-[2-(1-Benzhydryl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea

1-[2-(1-Benzyl-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea

1-[2-(1-Benzyl-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[6,7-Dimethoxy-1-(1-phenyl-propyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[6,7-Dimethoxy-1-(1-phenyl-propyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-4,4-dimethyl-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[(*R*)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[(*R*)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[(*R*)-1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[7-Benzyloxy-1-(3,4-dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-(3,4-Dichloro-benzyl)-6-methoxy-2-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid methylamide

1-(3,4-Dichloro-benzyl)-6-methoxy-2-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid propylamide

1-(3,4-Dichloro-benzyl)-6-methoxy-2-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid dimethylamide

1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(7-methyl-[1,8]naphthyridin-4-yl)-urea

1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(5,6,7,8-tetrahydro-quinolin-4-yl)-urea

1-[2-(Benzyl-methyl-amino)-pyridin-4-yl]-3-{2-[1-(4-fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-urea

1-[2-(Benzyl-methyl-amino)-6-methyl-pyridin-4-yl]-3-{2-[1-(4-fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-urea

1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-[2-(methyl-phenyl-amino)-pyridin-4-yl]-urea

1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-pyrrolidin-1-yl-pyridin-4-yl)-urea

1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methylamino-1-yl-pyridin-4-yl)-urea

Quinolin-4-yl-carbamic acid 2-(6,7-dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl ester

Quinolin-4-yl-carbamic acid 2-(1-benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl ester

Quinolin-4-yl-carbamic acid 2-[1-(4-fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl ester

Quinolin-4-yl-carbamic acid 3-(1-benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-propyl ester

Quinolin-4-yl-carbamic acid 3-(6,7-dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-propyl ester

Quinolin-4-yl-carbamic acid 3-[1-(3,4-difluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl ester

Quinolin-4-yl-carbamic acid 3-[1-(3,4-dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl ester

Quinolin-4-yl-carbamic acid 3-[1-(4-fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl ester

Because of their ability to inhibit the actions of urotensin II, the described compounds can be used for treatment of diseases which are associated with an increase in vasoconstriction, proliferation or other disease states associated with the actions of urotensin II. Examples of such diseases are hypertension, atherosclerosis, angina or myocardial ischemia, congestive heart failure, cardiac insufficiency, cardiac arrhythmias, renal ischemia, chronic kidney disease, renal failure, stroke, cerebral vasospasm, cerebral ischemia, dementia, migraine, subarachnoidal hemorrhage, diabetes, diabetic arteriopathy, asthma, chronic obstructive pulmonary disease, high-altitude pulmonary edema, Raynaud's syndrome, portal hypertension, thyroid dysfunction, pulmonary edema, pulmonary hypertension, or pulmonary fibrosis. They can also be used for prevention of restenosis after balloon or stent angioplasty, cancer, prostatic hypertrophy, erectile dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, gram negative septicemia, shock, sickle cell anemia, glomerulonephritis, renal colic, glaucoma, therapy and prophylaxis of diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, pain, addictions, schizophrenia, Alzheimer's disease, anxiety, obsessive-compulsive behavior, epileptic seizures, stress, depression, dementias, neuromuscular disorders, neurodegenerative diseases, as well as other diseases related to a dysregulation of urotensin II or urotensin II receptors.

These compositions may be administered in enteral or oral form e.g. as tablets, dragees, gelatine capsules, emulsions, solutions or suspensions, in nasal form like sprays or rectally in form of suppositories. These compounds may also be administered in intramuscular, parenteral or intravenous form, e.g. in form of injectable solutions.

These pharmaceutical compositions may contain the compounds of formula 1 as well as their pharmaceutically acceptable salts in combination with inorganic and/or organic excipients, which are usual in the pharmaceutical industry, like lactose, maize or derivatives thereof, talcum, stearic acid or salts of these materials.

For gelatine capsules vegetable oils, waxes, fats, liquid or half-liquid polyols etc. may be used. For the preparation of solutions and sirups e.g. water, polyols, saccharose, glucose etc. are used. Injectables are prepared by using e.g. water, polyols, alcohols, glycerin, vegetable oils, lecithin, liposomes etc. Suppositories are prepared by using natural or hydrogenated oils, waxes, fatty acids (fats), liquid or half-liquid polyols etc.

The compositions may contain in addition preservatives, stabilisation improving substances, viscosity improving or regulating substances, solubility improving substances, sweeteners, dyes, taste improving compounds, salts to change the osmotic pressure, buffer, anti-oxidants etc.

The compounds of general formula 1 may also be used in combination with one or more other therapeutically useful substances e.g. α- and β-blockers like phentolamine, phenoxybenzamine, atenolol, propranolol, timolol, metoprolol, carteolol, carvedilol, etc.; with vasodilators like hydralazine, minoxidil, diazoxide, flosequinan, etc.; with calcium-antagonists like diltiazem, nicardipine, nimodipine, verapamil, nifedipine, etc.; with angiotensin converting enzyme-inhibitors like cilazapril, captopril, enalapril, lisinopril etc.; with potassium channel activators like pinacidil, chromakalim, etc.; with angiotensin receptor antagonists like losartan, valsartan, candesartan, irbesartan, eprosartan, telmisartan, and tasosartan, etc.; with diuretics like hydrochlorothiazide, chlorothiazide, acetolamide, bumetanide, furosemide, metolazone, chlortalidone, etc.; with sympatholytics like methyldopa, clonidine, guanabenz, reserpine, etc.; with endothelin receptor antagonists like bosentan, tezosentan, darusentan, atrasentan, enrasentan, or sitaxsentan, etc.; with anti-hyperlipidemic agents like lovastatin, pravistatin, fluvastatin, atorvastatin, cerivastatin, simvastatin, etc.; and other therapeutics which serve to treat high blood pressure, vascular disease or other disorders listed above.

The dosage may vary within wide limits but should be adapted to the specific situation. In general the dosage given daily in oral form should be between about 3 mg and about 3 g, preferably between about 10 mg and about 1 g, especially preferred between 5 mg and 300 mg, per adult with a body weight of about 70 kg. The dosage should be administered preferably in 1 to 3 doses of equal

weight per day. As usual children should receive lower doses which are adapted to body weight and age.

Compounds of the general formula 1 can be prepared using methods generally known in the art, according to the general sequence of reactions outlined below. For simplicity and clarity reasons sometimes only a few of the possible synthetic routes that lead to compounds of general formula 1 are described.

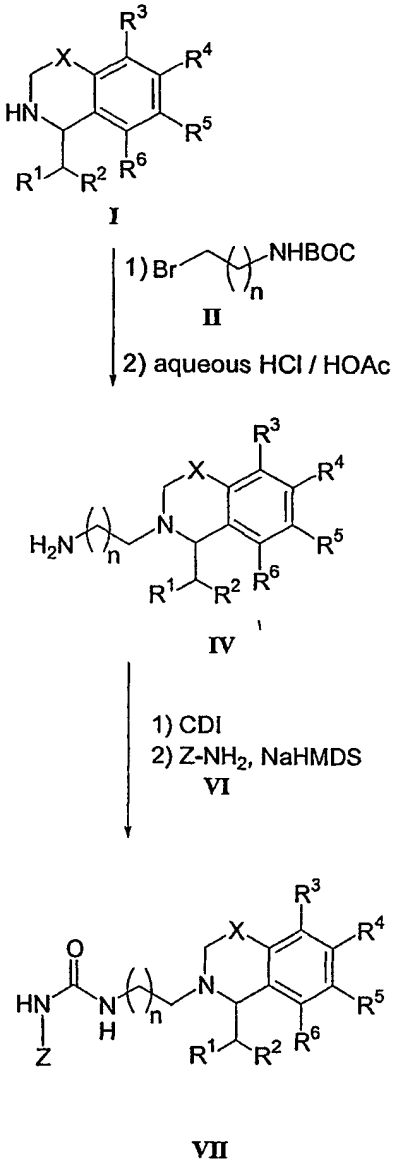
For the synthesis of compounds of general formula 1 general synthetic routes illustrated in Schemes A through E can be employed. In some instances one or another of the various groups (R^1 to R^9, X, Y, Z, n) might be incompatible with the assembly illustrated in Schemes A through E and so will require the use of protecting groups. The use of protecting groups is well known in the art (see for example "Protective Groups in Organic Synthesis, T.W. Greene, Wiley-Interscience, 1981). Particular groups that may require protection are amines (protected as amides or carbamates), alcohols (protected as esters or ethers) and carboxylic acids (protected as esters). For the purposes of this discussion, it will be assumed that such protecting groups as are necessary are in place.

1,2,3,4-Tetrahydroisoquinolines and 1,2,3,4-tetrahydrobenz[c]azepines of general structure I in Schemes A through C are either commercially available or are prepared in racemic or optically active form by methods well known in the art. For instance they can be prepared by a ring-closing condensation reaction of amides derived from the corresponding phenylethylamines or phenylpropylamines and the appropriate carboxylic acid under the action of $POCl_3$ or PCl_5, followed by treatment with a reducing agent such as $NaBH_4$ (Whaley WM, Govindachari TR "The preparation of 3,4-dihydroisoquinolines and related compounds by the Bischler-Napieralski reaction." Org. React. (1951) 6, 74-106. Finkelstein J, Chiang E, Brossi A "Synthesis of 1,2,3,4-tetrahydro-1,1,2,3,3,4,4,-heptamethyl-6,7-dimethoxyisoquinoline and related compounds as potential hypotensive agents." J. Med. Chem. (1971) 14, 584-588. Ukaji Z, Shimizu Y, Kenmoku Y, Ahmend A, Inomata K "Catalytic asymmetric addition of dialkylzinc to 3,4-dihydroisoquinoline N-oxides utilizing tartaric acid ester as a chiral auxiliary." Bull. Chem. Soc. Jpn. (2000), 73, 447-452. Zheng W, Nikulin VI,

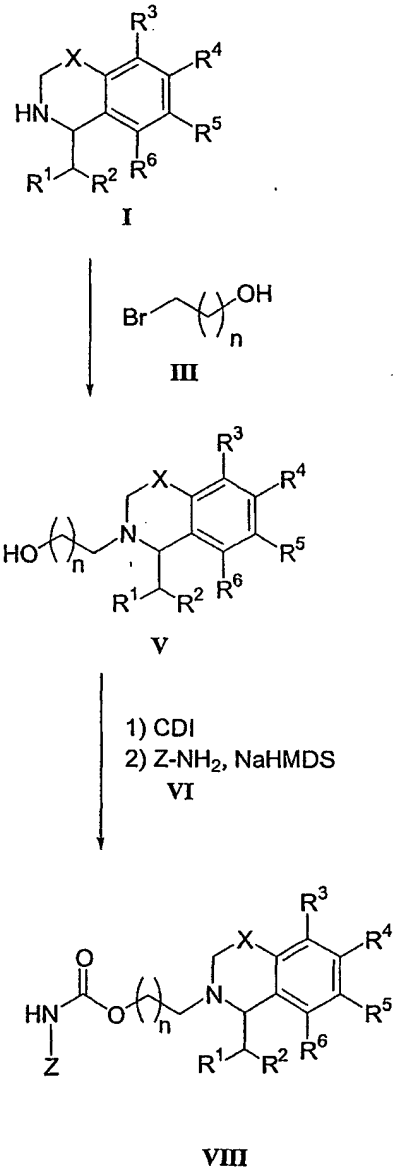
Konkar AA, Vansal SS, Shams G, Feller DR, Miller DD "2-Amino-4-benzyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridines: novel selective beta3-adrenoceptor antagonists." J Med Chem (1999), 42, 2287-2294). Substantially enantiomerically pure 1-substituted-2-tetrahydroisoquinoline and 1-substituted-2-tetrahydrobenzazepine derivatives are prepared by analogous methods (Polniaszek R.P. et al., J. Am. Chem. Soc. (1989) 111, 4859-4863). The key step of this asymmetric synthesis is a stereoselective hydride reduction of a chiral iminium ion obtained by *Bischler-Napieralski* reaction. For the preparation of (*R*)-1-substituted-2-tetrahydroisoquinoline derivatives the chirality resident in the substrate is derived from commercially available (*R*)-(+)-α-phenethylamine.

According to schemes A or B, appropriate 1,2,3,4-tetrahydroisoquinolines or 1,2,3,4-tetrahydrobenz[c]azepines of general structure I are N-alkylated with suitably protected aminoalkyl halides II or hydroxyalkyl halides III. Removal of the protecting group provides the amines IV or alcohols V. The intermediates IV and V are further elaborated to the final compounds of general formula 1 by stepwise treatment with a carbonylating agent such as carbonyldiimidazole, followed by reaction with a suitable amine VI in the presence of a strong base such as sodium hexamethyldisilazide. This provides the final compounds VII and VIII, which correspond to general formula 1, in which Y is NH or O, respectively, and in which n, X, Z and R^1 to R^6 have the definitions given in general formula 1.

SCHEME A:



SCHEME B:



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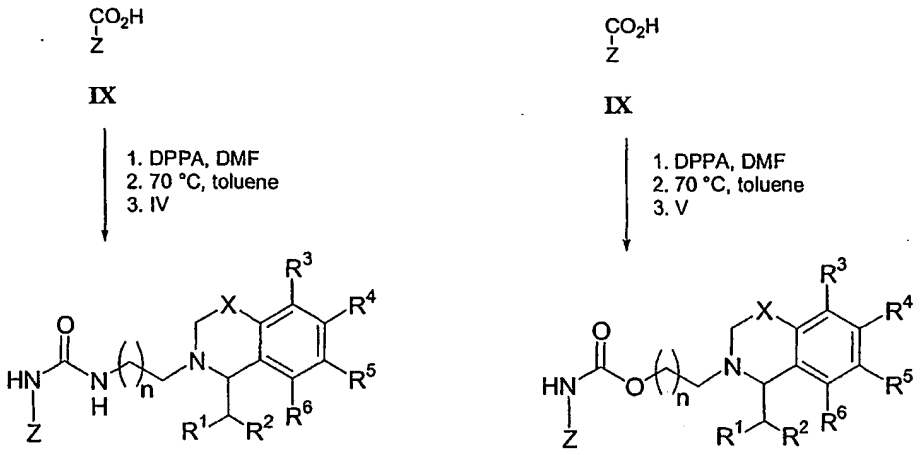
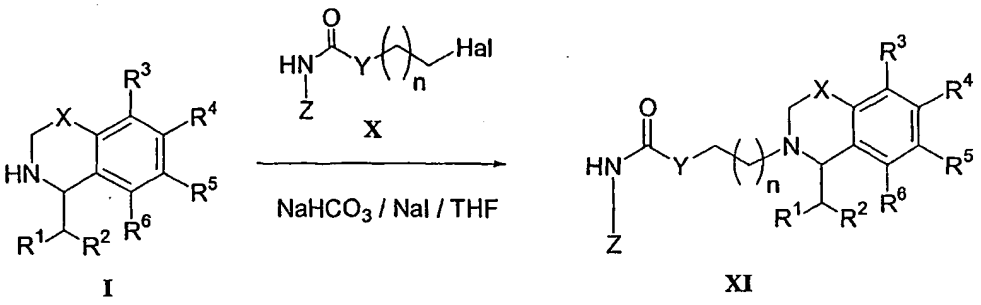
Scheme C:



An alternative synthetic route to compounds of general formula 1 is illustrated in Scheme C. Thus, carboxylic acids of general structure IX are converted to their corresponding acyl azide, for example by the treatment with DPPA in a polar aprotic solvent such as DMF. The crude acyl azide is subjected to thermal rearrangement in an inert solvent such as toluene, to provide the corresponding isocyanate. Reaction of the crude isocyanate with alkyl amines of general structure IV or with alkyl alcohols of general structure V provides the target compounds VII or VIII in which n, X, Y, Z and R^1 to R^6 have the definitions given in general formula 1.

An alternative synthetic route to compounds of general formula 1 is illustrated in Scheme D. Thus, 1,2,3,4-tetrahydroisoquinolines of general structure I are N-alkylated with compounds of general structure X (Russell RK et al. "Thiophene Systems. 9 Thienopyrimidinedione Derivatives as Potential Antihypertensive Agents" J Med Chem 1988, 31, 1786-1793) in an aprotic solvent such as THF in the presence of a scavenger base such as $NaHCO_3$ or di-isopropylethylamine, to provide the target compounds XI in which n, X, Y, Z and R^1 to R^6 have the definitions given in general formula 1.

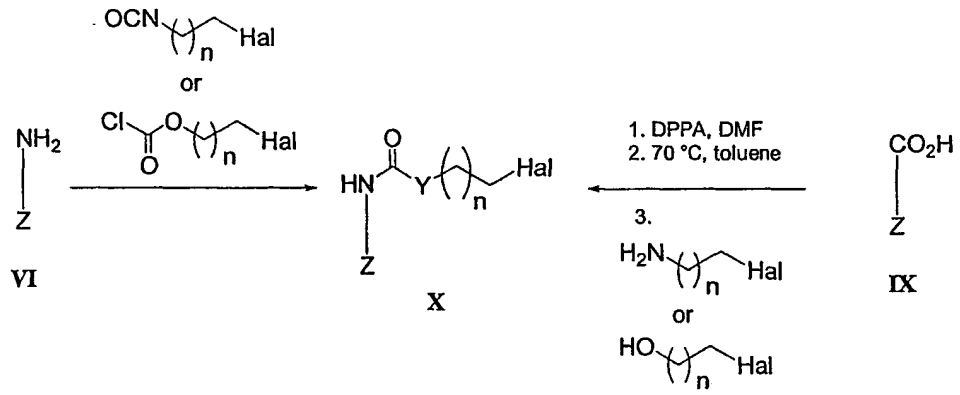
Scheme D:



I X XI

The preparation of the requisite intermediates of general structure X is illustrated in Scheme E, wherein Y, Z and n have the meaning given in general formula 1, and Hal stands for a halogen atom such as chloride. Commercially available or well-known heteroaryl amines of general structure VI are reacted with commercially available or well-known haloalkyl isocyanates, or haloalkyl chloroformates. Alternatively, compounds of general structure X are prepared by reaction of the isocyanate derived from heteroaryl carboxylic acids IX.

SCHEME E:



VI X IX

The foregoing general description of the invention will now be further illustrated by a number of examples which do not at all limit the scope of the invention.

EXAMPLES

LIST OF ABBREVIATIONS:

AcOH	acetic acid
BSA	bovine serum albumin
CDI	carbonyldiimidazole
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphorylazide
EDC	*N*-(3-dimethylaminopropyl)-*N'*-ethyl-carbodiimide
EDTA	ethylenediamine tetra-acetic acid
EtOAc	ethyl acetate
Et_2O	diethyl ether
Hex	hexane
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HV	high vacuum conditions
LC-MS	liquid chromatography-mass spectroscopy
LAH	lithium aluminum hydride
MeOH	methanol

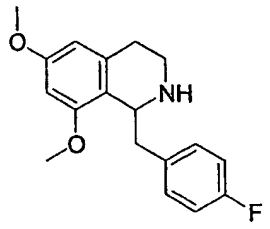
min	minutes
MHz	megahertz
NaHMDS	sodium bis(trimethylsilyl)amide
NMR	nuclear magnetic resonance
ppm	part per million
PBS	phosphate-buffered saline
PyBOP	(benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate
rt	room temperature
sat.	saturated
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
t_R	retention time

Reactions are routinely performed under an inert atmosphere such as N_2 gas in air. dried glassware. Solvents are used as received from the vendor. Evaporations are performed in a rotary evaporator at reduced pressure and a water bath temperature of 50 °C. LC-MS characterizations are performed on a Finnigan HP1100 platform using ESI ionization mode, and positive ion detection with a Navigator AQA detector. Analytical liquid chromatographic separations are performed on a C18 column of 4.6 x 30 mm dimensions and a mobile phase consisting of a 6 minute gradient of 2 – 95% CH_3CN in water containing 0.5% formic acid at a flow rate of 0.45 mL/min. Retention time (t_R) is given in min. TLC is performed on pre-coated silica gel 60 F_{254} glass-backed plates (Merck).

Preparative HPLC is performed on a Varian/Gilson platform using a C18 column of 21 x 60 mm dimensions and a mobile phase consisting of a gradient of 2 - 95% CH_3CN in water containing 0.5% formic acid.

Preparation of Intermediates. Example A.

A1. (4-Fluoro-benzyl)-6,8-dimethoxy-1,2,3,4-tetrahydro-isoquinoline.



2-(3,5-Dimethoxy-phenyl)-ethylamine.

To a suspension of $LiAlH_4$ (1.76 g, 46.4 mmol) in THF (30 mL) is added at 0°C dropwise a solution of 1,3-dimethoxy-5-(2-nitro-vinyl)-benzene (2.43 g, 11.6 mmol; Gairaud CB, Lappin GR, J Org Chem 1953, 18, 1) in THF (70 mL). The mixture is stirred for 30 min at this temperature and then at reflux for 4 h. The reaction mixture is quenched by the subsequent addition of 2 N NaOH (20 mL) and stirred for another 15 min at ambient temperature. The aqueous solution is extracted three times with EtOAc. The combined organic layers are dried with anhydrous $MgSO_4$, filtered and concentrated to give the title compound as a yellow oil.

N-[2-(3,5-Dimethoxy-phenyl)-ethyl]-2-(4-fluoro-phenyl)-acetamide.

To a solution of 2-(3,5-dimethoxy-phenyl)-ethylamine (1.01 g, 5.57 mmol) in anhydrous DMF (50 mL) is added 4-fluorophenyl acetic acid (860 mg, 5.57mmol), PyBOP (3.17 g) and N-ethyldiisopropylamine (2.2 mL, 12.8 mmol). The mixture is stirred at rt for 14 h. Water (60 mL) is added, and the mixture is extracted with EtOAc (4 x 60 mL). The combined organic phases are washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by silica gel column chromatography (EtOAc/Hex, 7:3) to afford the title compound as a yellow oil.

1-(4-Fluoro-benzyl)-6,8-dimethoxy-1,2,3,4-tetrahydro-isoquinoline.

To a stirred solution of *N*-[2-(3,5-dimethoxy-phenyl)-ethyl]-2-(4-fluoro-phenyl)-acetamide (404 mg, 1.27 mmol) in CH_3CN (3 mL) is added $POCl_3$ (350 µL, 3.82 mmol). The reaction mixture is stirred at reflux for 30 min. Concentration under reduced pressure gives a residual oil, which is dissolved in MeOH (10 mL). To this solution is added portionwise $NaBH_4$ (340 mg, 8.61 mmol) at 0°C The reaction mixture is allowed to warm to rt and is stirred for 14 h. The reaction mixture is poured into water (15 mL) and extracted four times with CH_2Cl_2. The combined organic layers are dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue is purified by flash column chromatography (CH_2Cl_2 / MeOH, 9:1) to give the title compound as a brown oil.

Examples A2 - A4.

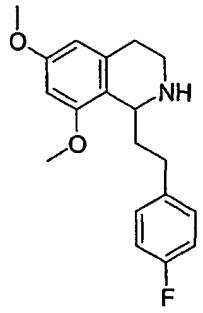
The following starting materials are prepared by the method of example A1:

A2. 1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A3. 1-(3,4-Difluoro-benzyl)-6,8-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A4. 1-(3-Fluoro-4-methoxy-benzyl)-6,8-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A5. 1-[2-(4-Fluoro-phenyl)-ethyl]-6,8-dimethoxy-1,2,3,4,-tetrahydro-isoquinoline.



N-[2-(3,5-Dimethoxy-phenyl)-ethyl]-3-(4-fluoro-phenyl)-propionamide.

2-(3,5-Dimethoxy-phenyl)-ethylamine (1.20 g, 6.62 mmol) is dissolved in anhydrous DMF (50mL), and 3-(4-fluorophenyl) propionic acid (1.113 g, 6.62 mmol), PyBOP (3.77 g) and DIPEA (2.61 mL, 15 mmol) are added. The mixture is stirred at rt for 14 h. Water (60 mL) is added, and the mixture is extracted with EtOAc (4 x 60 mL). The combined organic phases are washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by silica gel column chromatography (EtOAc/Hex, 7:3) to afford the title compound as a yellow oil.

1-[2-(4-Fluoro-phenyl)-ethyl]-6,8-dimethoxy-1,2,3,4,-tetrahydro-isoquinoline.

To a stirred solution of *N*-[2-(3,5-dimethoxy-phenyl)-ethyl]-3-(4-fluoro-phenyl)-propionamide (1.25 g, 3.77 mmol) in CH_3CN (12 mL) is added $POCl_3$ (1.04 mL, 11 mmol). The reaction mixture is stirred at reflux for 30 min. Concentration under reduced pressure gives a residual oil, which is dissolved in MeOH (35 mL). To this solution is added portionwise $NaBH_4$ (1.00 g, 26.4 mmol) at 0°C and the reaction mixture is allowed to warm to rt and stir for 14 h. The mixture is poured into water (40 mL) and extracted with CH_2Cl_2 (4 x 40 mL). The combined organic layers are dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue is purified by flash column chromatography (CH_2Cl_2/MeOH, 9:1) to give the title compound as a brown oil.

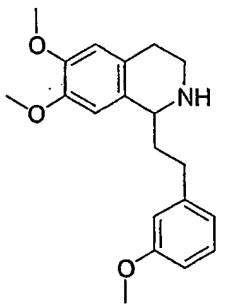
Examples A6 - A7.

The following starting materials are prepared according to the method of example A5:

A6. 1-[2-(2,4-Difluoro-phenyl)-ethyl]-6,8-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A7. 1-[2-(3,4-Difluoro-phenyl)-ethyl]-6,8-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A8. 6,7-Dimethoxy-1-[2-(3-methoxy-phenyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline.



N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3-(3-methoxy-phenyl)-propionamide.

To a suspension of 3-(3-methoxy-phenyl)-propionic acid (1.19 g, 6.62 mmol) and 3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride (1.33 g, 6.95 mmol) in THF (20 mL) is added 2-(3,4-dimethoxy-phenyl)-ethylamine (1.20 g, 6.62 mmol). The mixture is stirred at rt for 14 h. The mixture is poured onto H_2O (100 mL) and EtOAc (100 mL). The organic layer is washed successively with saturated sodium hydrogen carbonate solution, 10 % citric acid and saturated sodium chloride solution. The resulting organic layer is concentrated under reduced pressure to give the title compound.

6,7-Dimethoxy-1-[2-(3-methoxy-phenyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline.

To a solution of N-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-(3-methoxy-phenyl)-propion-amide (2.21 g, 6.44 mmol) in THF (50 mL) is added $POCl_3$ (4.91 g, 32.2 mmol) and the resulting solution is refluxed for 1 h. After cooling to rt the solvent is removed under reduced pressure. The resulting oil is treated with methanol (20 mL) and evaporated again. The residue is dissolved in absolute methanol (40 mL) cooled to 0°C and NaBH4 (1.21 g, 32.0 mmol) is added in portions. The resulting mixture is stirred at rt for 16 h, and then evaporated. To this residue is added water (150 mL). The aqueous layer is extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts are dried over $MgSO_4$ and concentrated to give the title compound.

Examples A9 - A45.

The following starting materials are prepared according to the method of example A8:

A9. 1-[(*E*)-2-(2,3-Difluoro-phenyl)-vinyl]-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A10. 1-[(*E*)-2-(2,4-Difluoro-phenyl)-vinyl]-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A11. 1-[(*E*)-2-(2,5-Difluoro-phenyl)-vinyl]-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A12. 1-[2-(2,5-Bis-trifluoromethyl-phenyl)-ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A13. 1-[2-(2,5-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A14. 1-[2-(3,4-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A15. 1-[2-(3,4-Dimethoxy-phenyl)-ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A16. 1-[2-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A17. 1-[2-(4-Fluoro-phenyl)-ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A18. 6,7-Dimethoxy-1-[2-(2-methoxy-phenyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline

A19. 6,7-Dimethoxy-1-[2-(4-methoxy-phenyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline

A20. 6,7-Dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-1,2,3,4-tetrahydro-isoquinoline

A21. 6,7-Dimethoxy-1-phenethyl-1,2,3,4-tetrahydro-isoquinoline

A22. 1-(2,5-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A23. 1-(2,6-Dichloro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A24. 1-(3,4-Difluoro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A25. 1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydro-isoquinoline

A26. 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A27. 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline

A28. 1-(3-Fluoro-4-methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A29. 1-(3-Fluoro-5-trifluoromethyl-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A30. 1-(4-Chloro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A31. 1-(4-Fluoro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A32. 1-Benzhydryl-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A33. 1-Benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A34. 1-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A35. 6-(3,4-Dimethoxy-benzyl)-2,3,6,7,8,9-hexahydro-[1,4]dioxino[2,3-g]-isoquinoline

A36. 6,7-Dimethoxy-1-(1-phenyl-propyl)-1,2,3,4-tetrahydro-isoquinoline

A37. 6,7-Dimethoxy-1-(2,3,4-trimethoxy-benzyl)-1,2,3,4-tetrahydro-isoquinoline

A38. 6,7-Dimethoxy-1-(3,4,5-trimethoxy-benzyl)-1,2,3,4-tetrahydro-isoquinoline

A39. 6,7-Dimethoxy-1-(3-methoxy-benzyl)-1,2,3,4-tetrahydro-isoquinoline

A40. 6,7-Dimethoxy-1-(4-methoxy-benzyl)-1,2,3,4-tetrahydro-isoquinoline

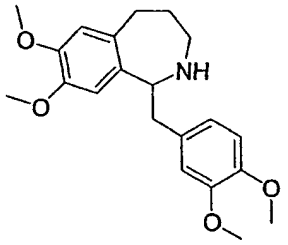
A41. 6,7-Dimethoxy-1-naphthalen-2-ylmethyl-1,2,3,4-tetrahydro-isoquinoline

A42. 6,7-Dimethoxy-1-phenoxymethyl-1,2,3,4-tetrahydro-isoquinoline

A43. 7-Benzyloxy-1-(3,4-dimethoxy-benzyl)-6-methoxy-1,2,3,4-tetrahydro-isoquinoline

A44. 1-(3,4-Dimethoxy-benzyl)-6-methoxy-1,2,3,4-tetrahydro-isoquinoline

A45. 1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-2,3,4,5-tetrahydro-1*H*-benzo[c]azepine.



3-(3,4-Dimethoxy-phenyl)-propionamide.

To a stirred solution of 3-(3,4-dimethoxy-phenyl)-propionic acid (10.0 g, 47.6 mmol) in dry THF (175 mL), under nitrogen, is added TEA (7.3 ml, 52.4 mmol). The resulting mixture is cooled to -10°C before ethyl chloroformate (5.0 ml, 52 mmol) is added dropwise. After stirring at -10°C (20 min), ammonium hydroxide (25% in water, 105 ml) in THF (105 mL) is added and the mixture is stirred at -15°C for 30 min and then at rt for 1.5 h. The reaction mixture is concentrated in vacuo, extracted three times with CH_2Cl_2 and the combined organic extracts are washed with saturated aqueous $NaHCO_3$ and brine. The organic phase is dried

over anhydrous $MgSO_4$, filtered and concentrated to give the title compound as a colorless solid.

3-(3,4-Dimethoxy-phenyl)-propylamine.

A solution of 3-(3,4-dimethoxy-phenyl)-propionamide (11.1 g, 53.0 mmol) in anhydrous THF (400 ml) is slowly added to a stirred, ice-cooled suspension of $LiAlH_4$ (4.02 g, 106 mmol) in anhydrous THF (170 mL). Upon completion of the addition, the mixture is stirred at reflux for 2 h. After cooling to 0°C, H_2O (5 mL) and NaOH 1N (5 mL) are added dropwise to decompose the excess of hydride. The suspension is filtered and evaporated. The residue is partitioned between H_2O (40 mL) and CH_2Cl_2 (100 mL). The organic layer is washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give the title compound as a yellow oil.

2-(3,4-Dimethoxy-phenyl)-*N*-[3-(3,4-dimethoxy-phenyl)-propyl]-acetamide.

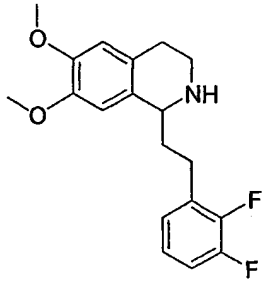
A solution of 3-(3,4-dimethoxy-phenyl)-propylamine (12.5 g, 64.1 mmol) and TEA (10 mL, 71.8 mmol) in anhydrous THF (70 mL) is cooled to 0°C and (3,4-dimethoxy-phenyl)-acetyl chloride (13.8 g, 64.1 mmol) in THF (28 mL) is added dropwise. After stirring at rt for 13 h under nitrogen, a saturated aqueous $NaHCO_3$ solution is added and the reaction mixture is extracted three times with EtOAc. The organic phase is dried over anhydrous $MgSO_4$, filtered and the solvent evaporated. The residue is washed with toluene and dried to give the title as a beige solid.

1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-2,3,4,5-tetrahydro-1*H*-benzo[c]azepine.

A mixture of 2-(3,4-dimethoxy-phenyl)-*N*-[3-(3,4-dimethoxy-phenyl)-propyl]-acetamide (6.16 g, 16.5 mmol) and $POCl_3$ (4.95 mL, 54.1 mmol) in anhydrous acetonitrile (185 mL) is stirred at reflux for 4 h under nitrogen. After cooling, the reaction mixture is evaporated and the residue is dissolved in MeOH (125 mL). The solution is cooled to 0°C and $NaBH_4$ (4.31 g, 114 mmol) is added portionwise. After stirring at 0°C for 2 h under nitrogen, the reaction mixture is poured into H_2O and extracted three times with CH_2Cl_2. The combined organic

extracts are washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to give a crude oil. Flash chromatography (CH_2Cl_2/MeOH: 9/1) yields the title compound as a yellow oil.

A46. 1-[2-(2,3-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline.



3-(2,3-Difluoro-phenyl)-propionic acid.

To a suspension of 2,3-difluoro-cinnamic acid (2.94 g, 16 mmol) in ethanol (100mL) is added Pd (10% on carbon, 50mg) and the mixture is treated with hydrogen (7.5 bar) for 15 h. The suspension is filtered through celite and the solvent evaporated to provide the title compound.

1-[2-(2,3-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline.

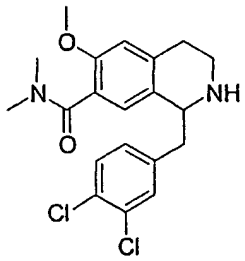
The compound is prepared from 3-(2,3-difluoro-phenyl)-propionic acid and 2-(3,4-dimethoxy-phenyl)-ethylamine according to the method of example A8.

Example A47.

The following starting material is prepared according to the method of example A46:

A47. 1-[2-(2,4-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A48. 1-(3,4-Dichloro-benzyl)-6-methoxy-1,2,3,4-tetrahydro-isoquinoline-7-carboxylic acid dimethylamide.



2-(4-Benzyloxy-3-methoxy-phenyl)-vinylamine.

A stirred suspension of LAH (8.0 g, 0.21 mol) in THF (300 mL) is cooled in an ice bath and a solution of 4-benzyloxy-3-methoxynitrostyrene (15.0 g, 52.6 mmol) in THF (300 mL) is added dropwise. The green reaction mixture is allowed to warm to room temperature over 0.5 h, and is then refluxed for 4 h. The grey reaction mixture is treated successively with water (8 mL), 15% aqueous NaOH (8 mL), and water (24 mL). The resulting gray suspension is stirred at 50 °C for 20 min. The resulting yellow suspension is filtered, and the residue is washed with EtOAc. The combined filtrates are evaporated to provide the title compound as yellow oil which is used without further purification.

N-[2-(4-Benzyloxy-3-methoxy-phenyl)-vinyl]-2-(3,4-dichloro-phenyl)-acetamide.

A mixture of 3,4-dichlorophenyl acetic acid (10.6 g, 51.7 mmol) and 2-(4-benzyloxyz-3-methoxy-phenyl)-vinylamine (12.1 g, 47 mmol) in toluene (100 mL) is heated at reflux in a Dean-Stark apparatus for 17 h. The reaction is allowed to cool to rt. Filtration yields the title compound as yellow crystals. The filtrate is heated again at reflux in a Dean-Stark apparatus for 16 h, and then allowed to cool to rt. Filtration provides a second portion of the title compound as yellow crystals. The two batches are combined and used without further purification.

7-Benzyloxy-1-(3,4-dichloro-benzyl)-6-methoxy-1,2,3,4-tetrahydro-isoquinoline.

To a suspension of N-[2-(4-benzyloxy-3-methoxy-phenyl)-vinyl]-2-(3,4-dichloro-phenyl)-acetamide (13.3 g, 30 mmol) in CH_3CN (100 mL) at rt is added dropwise

phosphoroxychloride (8.1 mL, 13.5 g, 88 mmol). The resulting white suspension is heated to reflux, and the resulting yellow solution is heated at reflux for 3 h. The dark yellow solution is allowed to cool and is evaporated to a yellow oil. The oil is taken up in MeOH (100 mL) and evaporated to yield an orange solid. The material is redissolved in MeOH (100 mL) and the solution is cooled to 0 °C. $NaBH_4$ (3.61 g, 95 mmol) is added in portions with gas evolution and a strong exotherm. The resulting white suspension is stirred at rt for 16 h. The reaction mixture is partitioned between EtOAc (200 mL) and water (200 mL), and the aqueous phase is extracted with EtOAc (3 x 200 mL). The combined organic phase is washed with water and brine, and evaporated to provide the title compound as a faint yellow oil which is used without further purification.

1-(3,4-Dichloro-benzyl)-6-methoxy-1,2,3,4-tetrahydro-isoquinolin-7-ol.

To a solution of 7-benzyloxy-1-(3,4-dichloro-benzyl)-6-methoxy-1,2,3,4-tetrahydro-isoquinoline (14.1 g, 30 mmol) in MeOH (150 mL) and 1,2-dichlorobenzene (30 mL) is added 50% Pd on charcoal (500 mg). The reaction vessel is flushed with nitrogen and then with hydrogen at atmospheric pressure. After stirring at rt for 16 h, the reaction mixture is filtered through Hyflo, and evaporated to yield to the title compound as a beige solid which is used without further purification.

1-(3,4-Dichloro-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid tert-butyl ester.

To a solution of 1-(3,4-dichloro-benzyl)-6-methoxy-1,2,3,4-tetrahydro-isoquinolin-7-ol (9.6 g, 28 mmol) in isopropanol (30 mL) is added dropwise 1 M aqueous NaOH (30 mL) and di-tert-butyl-dicarbonate (6.7 g, 30.8 mmol). The resulting brown solution is stirred at rt for 30 min, and the resulting yellow solution is partioned between EtOAc (50 mL) and water (50 mL). The organic phase is washed successively with water and with brine, and is evaporated to provide the title compound as yellow oil, which is used without further purification.

1-(3,4-Dichloro-benzyl)-6-methoxy-7-trifluoromethanesulfonyloxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid tert-butyl ester.

To a solution of 1-(3,4-dichloro-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid tert-butyl ester (12 g, 27 mmol) in CH_2Cl_2 (100 mL) is added Et_3N (3.8 mL, 27 mmol). The reaction mixture is cooled to 0 °C and trifluoromethanesulfonic anhydride (4.45 mL, 27 mmol) is added. The resulting yellow solution is stirred at rt 30 min, and is poured onto aqueous saturated $NaHCO_3$ (100 mL). The aqueous phase is extracted with CH_2Cl_2 (2 x 100 mL), and the combined organic phases are dried (MgSO4), filtered and evaporated to provide the title compound as yellow oil. Purification is achieved by crystallization from MeOH. The evaporated mother liquor furnishes additional material upon silica gel chromatography (heptane:Et2O, 9:1).

7-Cyano-1-(3,4-dichloro-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid tert-butyl ester.

A solution of 1-(3,4-dichloro-benzyl)-6-methoxy-7-trifluoromethanesulfonyloxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid tert-butyl ester (10 g, 17 mmol) in DMF (15 mL) standing over freshly dried 4 A molecular sieves is deoxygenated by bubbling with argon for 20 min. This solution is added to a deoxygenated suspension of zinc cyanide (4.6 g, 34 mmol) in DMF (15 mL) under argon. The resulting light brown suspension is placed in a 120 °C oil bath. Tetrakis-(triphenylphosphine)-palladium (1.0 g) is added, and the brown reaction mixture is stirred at 120 °C for 2 h. The reaction mixture is cooled to rt, and partitioned between EtOAc and saturated aqueous $NaHCO_3$. The mixture is filtered through Hyflo. The aqueous phase is extracted with EtOAc (3 x 40 mL). The combined organic phases are extracted with brine, dried over $MgSO_4$, filtered, and evaporated. The resulting yellow oil partially solidifies. The mixture is filtered and washed with Et_2O to provide the title compound as white crystals. Evaporation of the filtrate and silica gel chromatography (EtOAc:heptane, 1:4) provides additional title compound as white crystals.

1-(3,4-Dichloro-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinoline-2,7-dicarboxylic acid 2-tert-butyl ester.

To a solution of 7-cyano-1-(3,4-dichloro-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid tert-butyl ester (3.60 g, 8.06 mmol) in benzyl alcohol (10 mL) is added KOH (3.00 g), and the reaction mixture is stirred at 160°C for 0.5 h. The reaction mixture is allowed to cool to rt and is acidified with 2 M aqueous HCl. The reaction mixture is partitioned with EtOAc (3 x 20 mL). The combined organic phases are washed with brine, dried over $MgSO_4$, filtered, and evaporated to yield a yellow oil. Chromatography over silica gel with CH_2Cl_2:MeOH 19:1 and then with MeOH provides the title compound as yellow solid.

1-(3,4-Dichloro-benzyl)-7-dimethylcarbamoyl-6-methoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid tert-butyl ester.

To a solution of 1-(3,4-dichloro-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinoline-2,7-dicarboxylic acid 2-tert-butyl ester (1.0 g, 2.1 mmol) in CH_2Cl_2 (10 mL) is added dimethylamine hydrochloride (0.35 g, 4.3 mmol), HOBt (65 mg, 0.43 mmo), DMAP (52 mg, 0.43 mmol), and EDC hydrochloride (493 mg, 2.6 mmol). The reaction mixture was stirred at rt for 16 h. The fine yellow suspension is diluted with CH_2Cl_2 (10 mL), and is washed with 1 M aqueous HCl and saturated aqueous $NaHCO_3$. The organic phase is dried over $MgSO_4$, filtered and evaporated to give the title compound.

1-(3,4-Dichloro-benzyl)-6-methoxy-1,2,3,4-tetrahydro-isoquinoline-7-carboxylic acid dimethylamide.

A solution of 1-(3,4-dichloro-benzyl)-7-dimethylcarbamoyl-6-methoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid tert-butyl ester (1.0 g, 2.0 mmol) in 4 M HCl in dioxane is stirred at 0 °C for 1 h. The reaction mixture is evaporated to provide the title compound as a white solid.

Examples A49 -A50.

The following starting materials are prepared according to the method of example A48:

A49. 1-(3,4-Dichloro-benzyl)-6-methoxy-1,2,3,4-tetrahydro-isoquinoline-7-carboxylic acid methylamide

A50. 1-(3,4-Dichloro-benzyl)-6-methoxy-1,2,3,4-tetrahydro-isoquinoline-7-carboxylic acid propylamide

Examples A51 -A52.

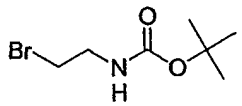
Enantiomerically pure starting materials are prepared according to the method of Polniaszek R.P. et al., J. Am. Chem. Soc. (1989) 111, 4859-4863.

A51. (*R*)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

A52. (*R*)-1-(4-Fluoro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline

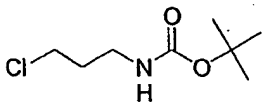
Preparation of Intermediates. Example B.

B1. (2-Bromo-ethyl)-carbamic acid tert-butyl ester.



To 1 N aqueous NaOH (200 mL) is added to MeOH (400 mL) and the resulting solution is cooled to 20 °C. 2-Bromoethylamine hydrobromide (25.0 g, 122 mmol) is added in a single portion, followed di-tert-butyl dicarbonate (26.6 g, 122 mmol). The reaction mixture is stirred for 2.5 h. The MeOH is removed on a rotary evaporator, and the aqueous suspension is extracted with CH_2Cl_2 (2 x 175 mL). The combined organic phases are extracted with 5% aqueous citric acid (300 mL), dried over $MgSO_4$, filtered, and evaporated to provide the title compound.

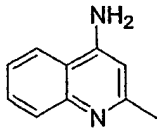
B2. (3-Chloro-propyl)-carbamic acid tert-butyl ester



This material is prepared analogously to example B1 from 3-chloropropylamine.

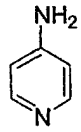
Preparation of Intermediates. Example C.

C1. 4-Amino-2-methylquinoline.



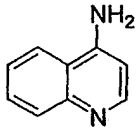
This material is commercially available.

C2. 4-Amino-pyridine.



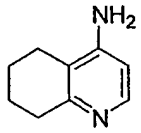
This material is commercially available.

C3. 4-Amino-quinoline.



Prepared from commercial 4-nitroquinoline *N*-oxide according to the method described in Shinkai H et al., "4-Aminoquinolines: Novel Nociceptin Antagonists with Analgesic Activity", J. Med. Chem. (2000) 43, 4667-4677.

C4. 4-Amino-6,7,8,9-tetrahydro-quinoline.



6,7,8,9-Tetrahydro-quinoline-*N*-oxide.

A solution of 5,6,7,8-tetrahydroquinoline (2.66 mL, 20 mmol) in THF (125mL) is cooled to 0°C and a solution of m-chloroperbenzoic acid (3.8g, 22 mmol) in THF (25 mL) is added. After 0.5 h the mixture is evaporated in vacuo and redissolved in CH_2Cl_2 (75mL). The solution is washed with NaOH (1M, 20mL) and citric acid (10%, 20mL), dried and evaporated to provide the title compound.

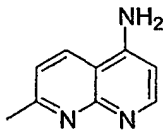
4-Nitro-6,7,8,9-tetrahydro-quinoline-*N*-oxide.

5,6,7,8-Tetrahydroquinoline-*N*-oxide (298 mg, 2 mmol) is treated with a cooled mixture of HNO_3 (100%, 0.5 mL) and H_2SO_4 (98%, 0.7 mL). The mixture is heated to 80°C for 2h, poured into ice (100 g) and extracted with CH_2Cl_2 (30mL). The organic phase is dreid and evaporated to provide the title compound.

4-Amino-6,7,8,9-tetrahydro-quinoline.

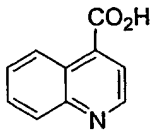
Prepared from 4-nitro-6,7,8,9-tetrahydro-quinoline-*N*-oxide according to the method of example C3.

C5. 4-Amino-7-methyl-[1,8]-naphthyridine.



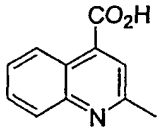
Prepared according to the method described in Barlin GB, Tan WL, "Potential Antimalarials. I 1,8-naphthyridines", Aust J Chem (1984) 37, 1065-1073. Radivov R, Haimova M, Simova E "Synthesis of 4-Amino-3-Pyridiyl and 4-Amino-5-Pyrimidyl Aryl Ketones and Related Compounds via an ortho-Lithiation Reaction", Synthesis (1986), 886-891.

C6. Quinoline-4-carboxylic acid.



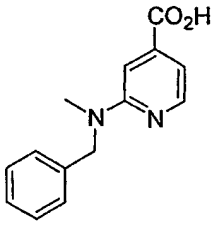
This material is commercially available.

C7. 2-Methyl-quinoline-4-carboxylic acid.



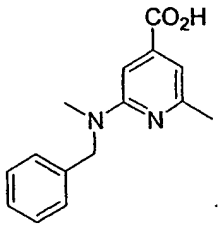
This material is prepared by reaction of isatin with acetone according to the method described in Brasyunas VB et al., "Synthesis of Quinoline-4-carboxylic acid and its derivatives", Chem. Heterocycl. Compd. (engl. Transl.) (1988) 670-673.

C8. 2-(Benzyl-methyl-amino)-isonicotinic acid.



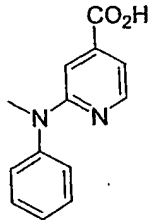
A mixture of 2-chloro-pyridine-4-carboxylic acid (300 mg, 1.9 mmol), benzylmethylamine (230 mg, 1.9 mmol) and triethylamine (192 mg, 1.9 mmol) is heated to 120°C for 12 h. The residue is dissolved in CH_2Cl_2 (30 mL) and extracted with 1M NaOH (3 x 5 mL). The aqueous phase is adjusted to pH 2 and extracted with EtOAc (6 x 5mL). The organic phases are combined, dried ($MgSO_4$), and evaporated to provide the title compound.

C9. 2-(Benzyl-methyl-amino)-6-methyl-isonicotinic acid.



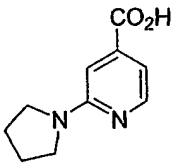
This material is prepared by reaction of 2-chloro-6-methyl-pyridine-4-carboxylic acid with benzylmethylamine analogously to example C8.

C10. 2-(Methyl-phenyl-amino)-isonicotinic acid.



This material is prepared by reaction of 2-chloro-pyridine-4-carboxylic acid with *N*-methylaniline analogously to example C8.

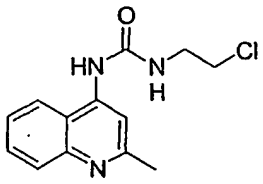
C11. 2-Pyrrolidin-1-yl-isonicotinic acid.



This material is prepared by reaction of 2-chloro-pyridine-4-carboxylic acid with pyrrolidine analogously to example C8.

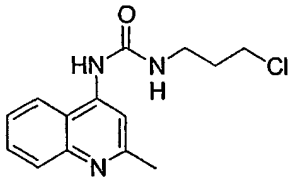
Preparation of Intermediates. Example D.

D1. 1-(2-Chloro-ethyl)-3-(2-methyl-quinolin-4-yl)-urea.



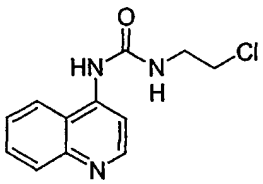
To a solution of 4-amino-2-methylquinoline (example C1, 12.6 g, 80 mmol) in THF (480 mL) is added 2-chloroethylisocyanate (10.2 mL, 120 mmol) at rt. The reaction mixture is stirred for 40 h at rt. MeOH (100 mL) is added, and stirring is continued an additional hour. The reaction mixture is evaporated and the residue is taken up in CH_2Cl_2. The organic phase is shaken with 1 N HCl (250 mL), and the resulting precipitate is collected by filtration. The solid is washed with CH_2Cl_2 (100 mL), saturated $NaHCO_3$ (2 x 100 mL), and with water (4 x 100 mL). The resulting solid is dried under HV at rt for 14 h to provide the title compound.

D2. 1-(3-Chloro-propyl)-3-(2-methyl-quinolin-4-yl)-urea.



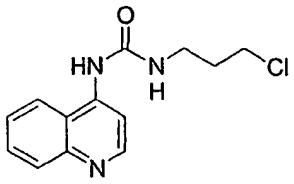
Analogously to method D1 the title compound is prepared from 4-amino-2-methylquinoline (example C1) and 3-chloropropylisocyanate.

D3. 1-(2-Chloro-ethyl)-3-(quinolin-4-yl)-urea.



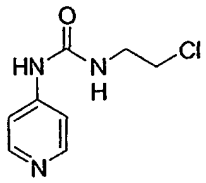
Analogously to method D1 the title compound is prepared from 4-amino-2-quinoline (example C3) and 2-chloroethylisocyanate.

D4. 1-(3-Chloro-propyl)-3-(quinolin-4-yl)-urea.



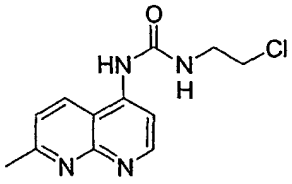
Analogously to method D1 the title compound is prepared from 4-amino-2-quinoline (example C3) and 3-chloropropylisocyanate.

D5. 1-(2-Chloro-ethyl)-3-(pyridin-4-yl)-urea.



Analogously to method D1 the title compound is prepared from 4-amino-pyridine (example C2) and 2-chloroethylisocyanate.

D6. 1-(2-Chloro-ethyl)-3-(7-methyl-[1,8]-naphthyridin -4-yl)-urea.

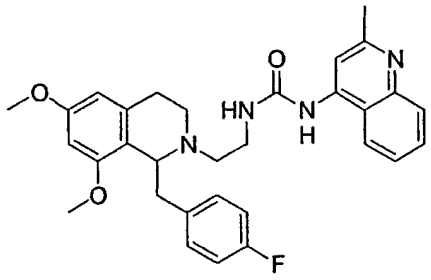


Analogously to method D1 the title compound is prepared from 4-amino-7-methyl-[1,8]-naphthyridine (example C5) and 2-chloroethylisocyanate.

PREPARATION OF FINAL PRODUCTS

Example 1.

1-{2-[1-(4-Fluoro-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea.



To a solution of 1-(4-fluoro-benzyl)-6,8-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (example A1, 50 mg, 0.16 mmol) in anhydrous THF (2.5 mL) is added 1-(2-chloro-ethyl)-3-(2-methyl-quinolin-4-yl)-urea (example D1, 43.8 mg, 0.16mmol), TEA (34.6 µL, 0.25 mmol) and NaI (2.5 mg, 0.017mmol). The mixture is stirred at 75°C for five days in a sealed flask. The reaction mixture is evaporated, and the residue is purified by preparative HPLC to provide the title compound.

LC-MS (MeCN / H_2O, 1:1) t_R = 0.93 min, m/z = 529.3 (M+1)

Examples 2-6.

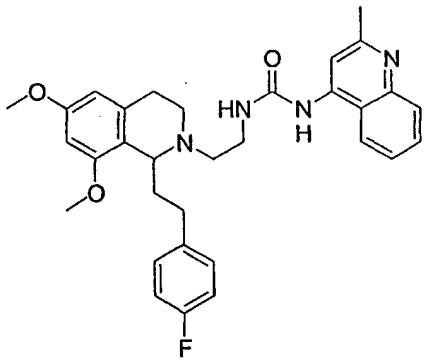
The additional examples set out in the following table are prepared starting from examples A1 to A4 and examples D1 or D3 using the method of example 1.

Example No	Example	t_R	$[M+H]^+$
2	1-{2-[1-(3,4-Difluoro-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	0.97	547.30
3	1-{2-[1-(3-Fluoro-4-methoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	1.05	559.70

4	1-{2-[1-(3,4-Difluoro-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	0.80	533.30
5	1-{2-[1-(3-Fluoro-4-methoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.13	545.24
6	1-{2-[1-(4-Fluoro-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	0.78	515.30

Example 7.

1-(2-{1-[2-(4-Fluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinoline-4-yl)-urea.



1-[2-(4-Fluoro-phenyl)-ethyl]-6,8-dimethoxy-1,2,3,4,-tetrahydro-isoquinoline (example A5, 100 mg, 0.317mmol) is dissolved in anhydrous THF (3.0mL), 1-(2-chloro-ethyl)-3-(2-methyl-quinolin-4-yl)-urea (example D1, 83.6 mg, 0.317mmol), TEA (66.2 µL, 0.475mmol) and NaI (4.8 mg, 0.032mmol) are added. The mixture is stirred at 75°C for five days in a sealed flask. The reaction mixture is evaporated, and the residue is purified by preparative HPLC to provide the title compound.

LC-MS (MeCN / H_2O, 1:1) t_R = 1.11 min, m/z = 543.5 (M+1)

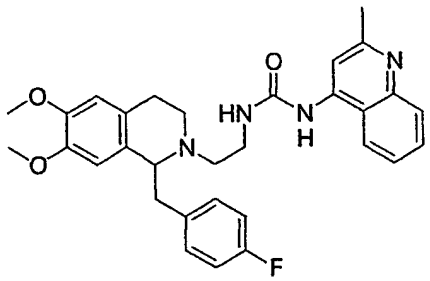
Examples 8-9.

The additional examples set out in the following table are prepared starting from examples A5 to A7 and examples D1 or D3 using the method of example 7.

Example No	Example	t_R	$[M+H]^+$
8	1-(2-{1-[2-(2,4-Difluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.16	561.34
9	1-(2-{1-[2-(2,4-Difluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-quinolin-4-yl-urea	1.15	547.32
10	1-(2-{1-[2-(3,4-Difluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.16	561.33
11	1-(2-{1-[2-(3,4-Difluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-quinolin-4-yl-urea	1.16	547.31
12	1-(2-{1-[2-(4-Fluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-quinolin-4-yl-urea	1.15	529.30

Example 13.

1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea.



To a solution of 1-(4-fluorobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (example A31, 0.16 g, 0.50 mmol) in THF (2 mL) is added 1-(2-chloroethyl)-3-(2-methylquinolin-4-yl)-urea (example D1, 0.18 g, 0.60 mmol), solid $NaHCO_3$ (50 mg, 0.6 mmol) and NaI (15 mg, 0.1 mmol). The mixture is stirred at 70 °C in a sealed flask for 5 days. The mixture is evaporated, and the residue is purified by preparative HPLC to provide the title compound.

LC-MS (MeCN / H_2O, 1:1) t_R = 1.10 min, m/z = 529.19 (M+1)

Examples 14-105.

The additional examples set out in the following table are prepared starting from examples A1 to A52 and examples D1 to D5 using the method of example 13.

Example No	Example	t_R	$[M+H]^+$
14	1-{2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	1.01	585.19
15	1-(2-{1-[(*E*)-2-(2,4-Difluoro-phenyl)-vinyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.13	559.31
16	1-(2-{1-[(*E*)-2-(2,5-Difluoro-phenyl)-vinyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.13	559.30
17	1-(2-{1-[2-(2,3-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.14	561.33
18	1-(2-{1-[2-(2,4-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.14	561.34
19	1-(2-{1-[2-(2,5-Bis-trifluoromethyl-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.18	661.30

20	1-(2-{1-[2-(2,5-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.14	561.32
21	1-(2-{1-[2-(3,4-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.14	561.32
22	1-(2-{1-[2-(3,4-Dimethoxy-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.09	585.37
23	1-(2-{1-[2-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.19	661.30
24	1-(2-{1-[2-(4-Fluoro-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.14	543.32
25	1-(2-{6,7-Dimethoxy-1-[2-(2-methoxy-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.13	555.36
26	1-(2-{6,7-Dimethoxy-1-[2-(3-methoxy-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.13	555.36
27	1-(2-{6,7-Dimethoxy-1-[2-(4-methoxy-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.13	555.37
28	1-(2-{6,7-Dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea	1.17	593.35
29	1-[2-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea	1.11	525.22
30	1-[2-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea	1.07	461.12

31	1-[2-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea	1.11	511.07
32	1-[3-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-propyl]-3-(2-methyl-quinolin-4-yl)-urea	1.11	539.26
33	1-[3-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-propyl]-3-quinolin-4-yl-urea	1.10	525.18
34	1-[2-(1-Benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea	1.14	555.21
35	1-[2-(1-Benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea	0.99	491.07
36	1-[2-(1-Benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea	1.06	541.07
37	1-[2-(1-Benzyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea	1.03	387.12
38	1-[2-(1-Benzyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea	1.10	437.08
39	1-[2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea	1.09	511.17
40	1-[2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea	0.98	447.10
41	1-[2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea	1.07	497.08
42	1-[2-(1-Benzyl-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea	1.06	417.09
43	1-[2-(1-Benzyl-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea	1.11	467.12

44	1-[2-(6,7-Dimethoxy-1-naphthalen-2-ylmethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea	1.10	497.10
45	1-[2-(6,7-Dimethoxy-1-naphthalen-2-ylmethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea	1.12	547.14
46	1-[2-(6,7-Dimethoxy-1-phenoxymethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea	0.98	463.09
47	1-[3-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-propyl]-3-(2-methyl-quinolin-4-yl)-urea	1.08	525.25
48	1-[3-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-propyl]-3-quinolin-4-yl-urea	1.04	511.17
49	1-{2-[1-(2,5-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea	1.04	507.10
50	1-{2-[1-(2,5-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.10	557.11
51	1-{2-[1-(2,6-Dichloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	1.12	579.26
52	1-{2-[1-(3,4-Difluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea	1.04	483.10
53	1-{2-[1-(3,4-Difluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.10	533.04
54	1-{2-[1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.10	587.11

55	1-{2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea	0.94	507.16
56	1-{2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.01	557.12
57	1-{2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(5,6,7,8-tetrahydro-quinolin-4-yl)-urea	0.83	561.30
58	1-{2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	1.11	571.21
59	1-{2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea	1.08	507.16
60	1-{2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.11	557.18
61	1-{2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea	1.02	477.10
62	1-{2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.08	527.10
63	1-{2-[1-(3-Fluoro-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	1.11	559.33
64	1-{2-[1-(3-Fluoro-5-trifluoromethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	1.15	597.33

65	1-{2-[1-(4-Chloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea	1.09	481.04
66	1-{2-[1-(4-Chloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.11	531.08
67	1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea	1.01	465.11
68	1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.09	515.06
69	1-{2-[6,7-Dimethoxy-1-(2,3,4-trimethoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea	1.00	537.17
70	1-{2-[6,7-Dimethoxy-1-(2,3,4-trimethoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.08	587.09
71	1-{2-[6,7-Dimethoxy-1-(3,4,5-trimethoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	1.12	601.29
72	1-{2-[6,7-Dimethoxy-1-(3,4,5-trimethoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea	0.96	537.09
73	1-{2-[6,7-Dimethoxy-1-(3,4,5-trimethoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.03	587.11
74	1-{2-[6,7-Dimethoxy-1-(3-methoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea	1.00	477.11
75	1-{2-[6,7-Dimethoxy-1-(3-methoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.08	527.10

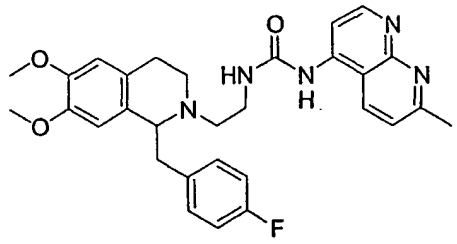
76	1-{2-[6,7-Dimethoxy-1-(4-methoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea	0.99	477.12
77	1-{2-[6,7-Dimethoxy-1-(4-methoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.07	527.11
78	1-{3-[1-(3,4-Difluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl}-3-quinolin-4-yl-urea	1.09	547.18
79	1-{3-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl}-3-(2-methyl-quinolin-4-yl)-urea	1.03	585.20
80	1-{3-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl}-3-quinolin-4-yl-urea	1.01	571.19
81	1-{3-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl}-3-(2-methyl-quinolin-4-yl)-urea	1.11	585.21
82	1-{3-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl}-3-quinolin-4-yl-urea	1.11	571.21
83	1-{3-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl}-3-quinolin-4-yl-urea	1.07	529.22
84	1-{2-[5-(3,4-Dimethoxy-benzyl)-7,8-dihydro-5*H*-[1,3]dioxolo[4,5-g]isoquinolin-6-yl]-ethyl}-3-pyridin-4-yl-urea	0.99	491.09
85	1-{2-[5-(3,4-Dimethoxy-benzyl)-7,8-dihydro-5*H*-[1,3]dioxolo[4,5-g]isoquinolin-6-yl]-ethyl}-3-quinolin-4-yl-urea	1.07	541.08
86	1-{2-[6-(3,4-Dimethoxy-benzyl)-2,3,8,9-tetrahydro-6*H*-[1,4]dioxino[2,3-g]isoquinolin-7-yl]-ethyl}-3-pyridin-4-yl-urea	1.00	505.07

87	1-{2-[6-(3,4-Dimethoxy-benzyl)-2,3,8,9-tetrahydro-6*H*-[1,4]dioxino[2,3-g]isoquinolin-7-yl]-ethyl}-3-quinolin-4-yl-urea	1.06	555.08
88	1-[2-(1-Benzhydryl-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea	1.14	573.11
89	1-[2-(1-Benzhydryl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea	1.10	523.07
90	1-[2-(1-Benzhydryl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea	1.12	573.08
91	1-[2-(1-Benzyl-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea	1.09	447.15
92	1-[2-(1-Benzyl-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea	1.13	497.09
93	1-{2-[1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.11	557.08
94	1-{2-[1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.14	557.12
95	1-{2-[6,7-Dimethoxy-1-(1-phenyl-propyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea	1.08	475.12
96	1-{2-[6,7-Dimethoxy-1-(1-phenyl-propyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.11	525.09
97	1-{2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-4,4-dimethyl-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.29	585.29
98	1-{2-[(*R*)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	1.05	571.35

99	1-{2-[(*R*)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea	1.01	557.14
100	1-{2-[(*R*)-1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	0.77	529.08
101	1-{2-[7-Benzyloxy-1-(3,4-dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	0.82	647.1
102	1-{2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea	0.77	541.13
103	1-(3,4-Dichloro-benzyl)-6-methoxy-2-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid methylamide	0.78	606.13
104	1-(3,4-Dichloro-benzyl)-6-methoxy-2-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid propylamide	0.82	634.04
105	1-(3,4-Dichloro-benzyl)-6-methoxy-2-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid dimethylamide	0.78	620.00

Example 106.

1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(7-methyl-[1,8]naphthyridin-4-yl)-urea.



106.1. {2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-carbamic acid tert-butyl ester.

To a solution of 1-(4-fluorobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (example A31, 1.05 g, 3.5 mmol) in THF (40 mL) is added (2-bromo-ethyl)-carbamic acid tert-butyl ester (example B1, 0.94 g, 4.2 mmol) and DIPEA. The reaction mixture is stirred at 70 °C in a sealed flask for 5 days. After cooling to rt, the reaction mixture is evaporated to dryness, and the residue is purified by preparative HPLC to provide the title compound.

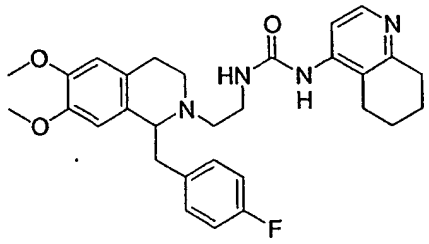
106.2. 1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(7-methyl-[1,8]naphthyridin-4-yl)-urea.

To a stirred solution of {2-[1-(4-fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-carbamic acid tert-butyl ester (example 106.1, 0.22 g, 0.5 mmol) in glacial AcOH (1 mL) is added conc. HCl (0.1 mL). After 5 min, the reaction mixture is partitioned with $CHCl_3$ (20 mL) and 1 N NaOH (15 mL). The organic phase is evaporated. The residue is taken up in DMSO (2 mL) and treated with CDI (0.2 g, 0.6 mmol, 1.2 eq). The reaction mixture is stirred at rt for 3 h, and then 4-amino-7-methyl-[1,8]-naphthyridine (example C5, 0.19 g, 0.6 mmol) is added. To the resulting solution is added in a single portion NaHMDS (2 M in THF, 1.25 mL, 2.5 mmol). The reaction mixture is stirred at rt for 30 min, then H_2O (0.4 mL) is added. The reaction mixture is evaporated and the residue purified by preparative HPLC to provide the title compound.

LC-MS (MeCN / H_2O, 1:1) t_R= 0.92 min, m/z = 530.3 (M+1)

Example 107.

1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(5,6,7,8-tetrahydro-quinolin-4-yl)-urea.

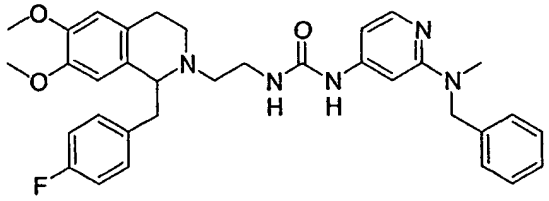


To a stirred solution of {2-[1-(4-fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-carbamic acid tert-butyl ester (example 106.1, 0.22 g, 0.5 mmol) in glacial AcOH (1 mL) is added conc. HCl (0.1 mL). After 5 min, the reaction mixture is partitioned between $CHCl_3$ (20 mL) and 1 N NaOH (15 mL). The organic phase is evaporated. The residue is taken up in DMSO (2 mL) and treated with CDI (0.2 g, 0.6 mmol, 1.2 eq). The reaction mixture is stirred at rt for 3 h, and then 4-amino-5,6,7,8-tetrahydroquinoline (example C4, 0.19 g, 0.6 mmol) is added. To the resulting solution is added in a single portion NaHMDS (2 M in THF, 1.25 mL, 2.5 mmol). The reaction mixture is stirred at rt for 30 min, then H_2O (0.4 mL) is added. The reaction mixture is evaporated and the residue purified by preparative HPLC to provide the title compound.

LC-MS (MeCN / H_2O, 1:1) t_R = 0.92 min, m/z = 519.3 (M+1)

Example 108.

1-[2-(Benzyl-methyl-amino)-pyridin-4-yl]-3-{2-[1-(4-fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-urea.



108.1 Benzyl-(4-isocyanato-pyridin-2-yl)-methyl-amine.

To a solution of 2-(benzyl-methyl-amino)-isonicotinic acid (example C8, 780 mg, 3.2 mmol) in DMF (10 mL) at 0°C is added triethylamine (360 mg, 3.5 mmol). After 5 minutes DPPA (975 mg, 3.5 mmol) is added, and stirring is continued for 2 h at 0°C and 12 h at 20 °C. The reaction is quenched with ice (10 g) and extracted with Et_2O (6 x 30 mL). The combined organic phases are washed successively with saturated $NaHCO_3$ (2 x 15 mL) and water (2 x 10 mL), and are evaporated without heating in vacuo. The residue is dissolved in dry toluene (16 mL) and heated to reflux for 2h. The resulting solution is carried forward without further isolation of the title compound.

108.2 1-[2-(Benzyl-methyl-amino)-pyridin-4-yl]-3-{2-[1-(4-fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-urea.

To a stirred solution of {2-[1-(4-fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-carbamic acid tert-butyl ester (example 106.1, 0.22 g, 0.5 mmol) in CH_2Cl_2 (1 mL) is added TFA (1 mL). After 2 h, the reaction mixture evaporated and partitioned between CH_2Cl_2 (20 mL) and 1 N NaOH (15 mL). The organic phase is dried ($MgSO_4$) and evaporated. The residue is dissolved in CH_2Cl_2 (2 mL) and added to a freshly prepared solution of benzyl-(4-isocyanato-pyridin-2-yl)-methyl-amine (example 108.1, 95.7 mg, 0.40 mmol) in toluene (2 mL). The mixture is stirred for 15 h at 20°C. Evaporation of the solvent and purification by HPLC provides the title compound.

LC-MS (MeCN / H_2O, 1:1) t_R = 0.73min, m/z = 584.3 (M+1)

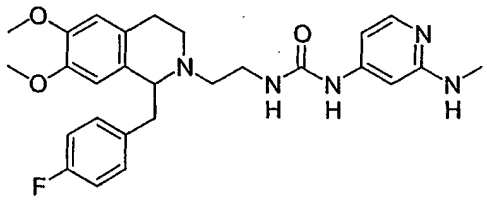
Examples 109-111.

The additional examples set out in the following table are prepared starting from example 106.1 and examples C9 to C11 using the method of example 108.

Example No	Example	t_R	$[M+H]^+$
109	1-[2-(Benzyl-methyl-amino)-6-methyl-pyridin-4-yl]-3-{2-[1-(4-fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-urea	0.76	598.43
110	1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-[2-(methyl-phenyl-amino)-pyridin-4-yl]-urea	0.80	570.10
111	1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-pyrrolidin-1-yl-pyridin-4-yl)-urea	0.77	534.09

Example 112.

1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methylamino-1-yl-pyridin-4-yl)-urea.

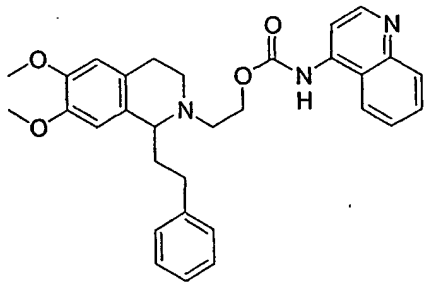


To a mixture of 1-[2-(benzyl-methyl-amino)-pyridin-4-yl]-3-{2-[1-(4-fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-urea (example 108, 0.12 g, 0.2 mmol) and Pd (10% on carbon, 20mg) in MeOH (10 mL) is added HCl (1N, 0.2 mL). A stream of hydrogen is passed through the solution for 0.5h and the solution is stirred under an atmosphere of hydrogen for 15 h. The solution is filtered and evaporated to provide the title compound.

LC-MS (MeCN / H_2O, 1:1) t_R = 0.77min, m/z = 534.09 (M+1)

Example 113.

(Quinolin-4-yl)-carbamic acid 2-(6,7-dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl ester.



113.1. 2-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethanol.

A solution of 6,7-dimethoxy-1-phenethyl-1,2,3,4-tetrahydro-isoquinoline (example A21, 59.5 mg, 0.2 mmol) and 2-bromoethanol (28.3 µL, 0.4 mmol) in tetrahydropyran (3 mL) is treated with DIPEA (68 µL, 0.4 mmol), and the reaction mixture is heated at 90 °C in a sealed flask for 5 days. The reaction is mixture evaporated to dryness, and the residue is purified by preparative HPLC, to provide the title compound.

113.2. (Quinolin-4-yl)-carbamic acid 2-(6,7-dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl ester.

To a solution of 2-(6,7-dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethanol (example 113.1, 29.7 mg, 0.087 mmol) in THF (1 mL) is added CDI (28.2 mg, 0.174 mmol, 2.0 eq). The reaction mixture is stirred at rt for 3 h, and then 4-amino-quinoline (example C3, 14 mg, 0.1 mmol) is added. To the resulting solution is added in a single portion NaHMDS (2 M in THF, 218 µL, 0.44 mmol). The reaction mixture is stirred at rt for 30 min, then H_2O / AcOH (9:1, 0.4 mL) is added. The reaction mixture is evaporated and the residue purified by preparative HPLC to provide the title compound.

LC-MS (MeCN / H_2O, 1:1) t_R = 1.17min, m/z = 512.19 (M+1)

Examples 114-120.

The additional examples set out in the following table are prepared starting from examples A1 to A52 and examples C1 to C3 using the method of example 113.

Example No	Example	t_R	$[M+H]^+$
114	Quinolin-4-yl-carbamic acid 2-(1-benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl ester	1.09	498.19
115	Quinolin-4-yl-carbamic acid 2-[1-(4-fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl ester	1.12	516.16
116	Quinolin-4-yl-carbamic acid 3-(1-benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-propyl ester	1.05	512.15
117	Quinolin-4-yl-carbamic acid 3-(6,7-dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-propyl ester	1.10	526.19
118	Quinolin-4-yl-carbamic acid 3-[1-(3,4-difluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl ester	1.10	548.18
119	Quinolin-4-yl-carbamic acid 3-[1-(3,4-dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl ester	1.10	572.25
120	Quinolin-4-yl-carbamic acid 3-[1-(4-fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl ester	1.08	530.12

Example 121.

IN VITRO BIOLOGICAL CHARACTERIZATION

The inhibitory activity of the compounds of general formula 1 on the actions of urotensin II can be demonstrated using the test procedures described hereinafter:

1) INHIBITION OF HUMAN [125I]-UROTENSIN II BINDING TO A RHABDOMYOSARCOMA CELL LINE

Whole cell binding of human [125I]-urotensin II is performed using human-derived TE-671 rhabdomyosarcoma cells (Deutsche Sammlung von Mikroorganismen und Zellkulturen, cell line #ACC-263), by methods adapted from a whole cell endothelin binding assay (Breu V et al., In vitro characterization of Ro-46-2005, a novel synthetic non-peptide antagonist of ET_A and ET_B receptors. FEBS Lett. 1993, 334, 210-214).

The assay is performed in 250 µL Dubecco's modified eagle medium, pH 7.4 (GIBCO BRL, CatNo 31885-023), including 25 mM HEPES (Fluka, CatNo 05473), 1.0 % DMSO (Fluka, CatNo 41644) and 0.5% (w/v) BSA Fraction V (Fluka, CatNo 05473) in polypropylene microtiter plates (Nunc, CatNo 442587). 300'000 suspended cells are incubated with gentle shaking for 4 h at 20°C with 20 pM human [125I]Urotensin II (Anawa Trading SA, Wangen, Switzerland, 2130Ci/mmol) and increasing concentrations of unlabeled antagonist. Minimum and maximum binding are derived from samples with and without 100 nM unlabelled U-II, respectively. After the 4 h incubation period, the cells are filtered onto GF/C filterplates (Packard, CatNo 6005174). The filter plates are dried, and then 50 µL scintillation cocktail (Packard, MicroScint 20, CatNo 6013621) is added to each well. The filterplates are counted in a microplate counter (Packard Bioscience, TopCount NXT).

All test compounds are dissolved and diluted in 100% DMSO. A ten-fold dilution into assay buffer is performed prior to addition to the assay. The final concentration of DMSO in the assay is 1.0%, which is found not to interfere with the binding. IC50 values are defined as the concentration of antagonist inhibiting

50% of the specific binding of [^{125}I]human U-II. Specific binding is the difference between maximum binding and minimum binding, as described above. An IC50 value of 0.206 nM is found for unlabeled human U-II. The compounds of the invention are found to have IC50 values ranging from 1 to 10000 nM in this assay. Specific examples have IC50's given in the following table.

Example	IC50 [nM]
20	67
22	63
29	125
58	550

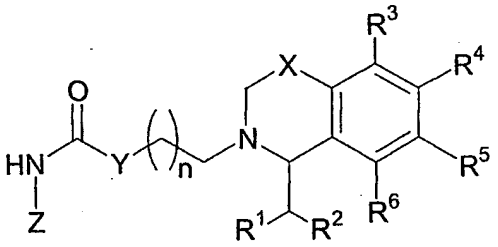
2) INHIBITION OF HUMAN UROTENSIN II-INDUCED CONTRACTIONS OF ISOLATED RAT AORTIC ARCH:

Adult Wistar rats are anesthetized (CO_2 inhalation) and exsanguinated. The aortic arch is excised, dissected and cut in 3 rings of 3 mm, ring #1 being the more proximal and ring #3 being the more distal. Each ring is suspended in a 10 mL isolated organ bath filled with Krebs-Henseleit solution (in mM; NaCl 115, KCl 4.7, $MgSO_4$ 1.2, KH_2PO_4 1.5, $NaHCO_3$ 25, $CaCl_2$ 2.5, glucose 10; pH 7.4) kept at 37° C and gassed with 95% O_2 and 5% CO_2. The rings are connected to force transducers and isometric tension is recorded (EMKA Technologies SA, Paris, France). The rings are stretched to a resting tension of 3g. Cumulative doses of human urotensin II (10^{-11} M to 10^{-6} M) are added after a 20 min incubation with the test compound or its vehicle (DMSO, 10 µL). An EC50 value of 1.09 ± 0.1 nM is found for unlabeled human U-II. The functional inhibitory potency of the test compound is assessed by calculating the pD_2' according to the formula: pD_2' = Log (*CR*-1) –Log [*B*], where *CR* is the ratio of the maximal effect without / with antagonist and [*B*] the concentration of the antagonist. Specific examples have pD2' values given in the following table:

Example	pD2'
29	5.23
93	5.45

CLAIMS

1. Compounds of the general formula 1,



General Formula 1

wherein

X represents $-CH_2-$, $-CH_2CH_2-$, $-C(CH_3)_2-$;

Y represents oxygen, NH;

n represents the numbers 1 or 2;

Z represents quinolin-4-yl which may be mono-substituted with lower alkyl in the positions 2, 6, or 8, or di-substituted with lower alkyl in the positions 2,6 or 2,8; [1,8]naphthyridin-4-yl which may be substituted in position 7 with lower alkyl; pyridin-4-yl which may be substituted in position 2 with R^7R^8N- and additionally in position 6 with hydrogen or lower alkyl;

R^1 represents naphthalen-1-yl; naphthalen-2-yl; benzo[1,3]dioxol-5-yl; benzyl, or mono-, di-, or tri-substituted benzyl substituted in the phenyl ring independently with lower alkyl, lower alkyloxy, trifluoromethyl, halogen, cyano; phenyl, or mono-, di- or tri-substituted phenyl, substituted independently with lower alkyl, lower alkyloxy, trifluoromethyl, halogen, cyano;

R^2 represents hydrogen, lower alkyl, aryl or forms with R^1 a styryl group of E or Z geometry, whereby the phenyl ring in the styryl group may be mono-, di- or tri-substituted phenyl, substituted independently with lower alkyl, lower alkyloxy, trifluoromethyl, halogen, cyano;

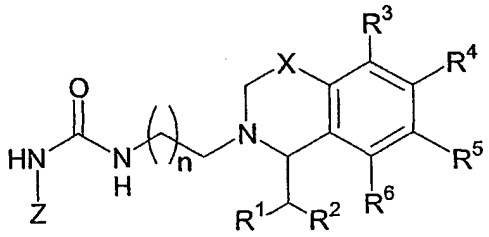
R^3, R^4, R^5 and R^6 independently represent hydrogen, cyano, hydroxy, lower alkyloxy, aralkyloxy, lower alkenyloxy, and R^5 additionally represents R^7R^8NCO;

R^4 and R^5 together may form with the phenyl ring a five- or a six-membered ring containing one or two oxygen atoms;

R^7 and R^8 independently represent hydrogen, lower alkyl, aryl, aralkyl, or together with the N form a pyrrolidine, piperidine, or morpholine ring;

and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, and mixtures of diastereomeric racemates; as well as their pharmaceutically acceptable salts, solvent complexes, and morphological forms.

2. Compounds of general formula 2,

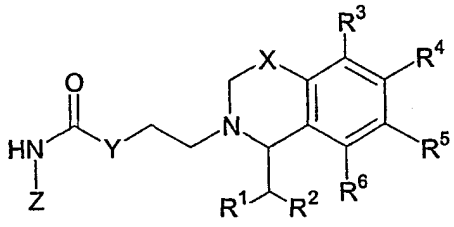


General Formula 2

wherein

R^1, R^2, R^3, R^4, R^5, R^6, X, Z, and n have the meaning given in general formula 1 above.

3. Compounds of general formula 3,

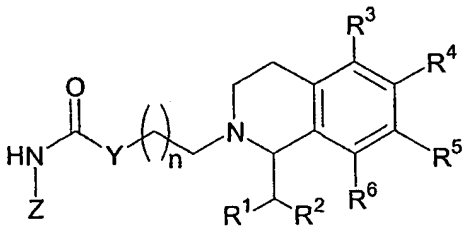


General Formula 3

wherein

R^1, R^2, R^3, R^4, R^5, R^6, X, Y, and Z have the meaning given in general formula 1 above.

4. Compounds of general formula 4,

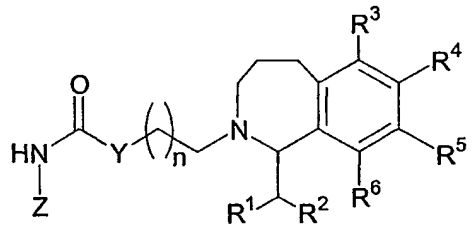


General Formula 4

wherein

R^1, R^2, R^3, R^4, R^5, R^6, Y, Z, and n have the meaning given in general formula 1 above.

5. Compounds of general formula 5,

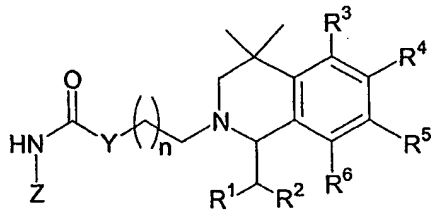


General Formula 5

wherein

R^1, R^2, R^3, R^4, R^5, R^6, Y, Z, and n have the meaning given in general formula 1 above.

6. Compounds of general formula 6,

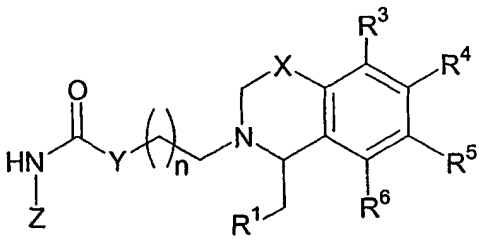


General Formula 6

wherein

R^1, R^2, R^3, R^4, R^5, R^6, Y, Z, and n have the meaning given in general formula 1 above.

7. Compounds of general formula 7,

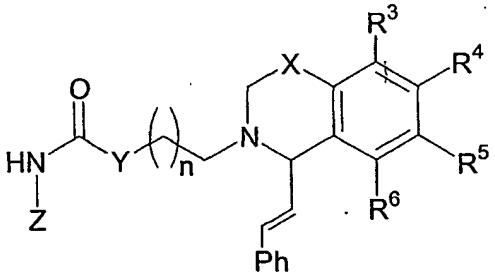


General Formula 7

wherein

R^1, R^3, R^4, R^5, R^6, X, Y, Z, and n have the meaning given in general formula 1 above.

8. Compounds of general formula 8,



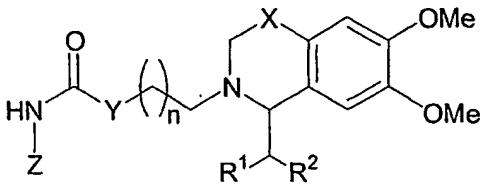
General Formula 8

wherein

Ph is phenyl; mono-, di- or tri-substituted phenyl, substituted independently with hydrogen, lower alkyl, lower alkyloxy, trifluoromethyl, halogen, or cyano;

R^3, R^4, R^5, R^6, X, Y, Z, and n have the meaning given in general formula 1 above.

9. Compounds of general formula 9,

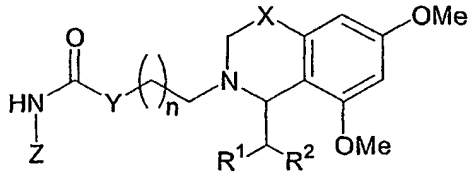


General Formula 9

wherein

R^1, R^2, X, Y, Z, and n have the meaning given in general formula 1 above.

10. Compounds of general formula 10,

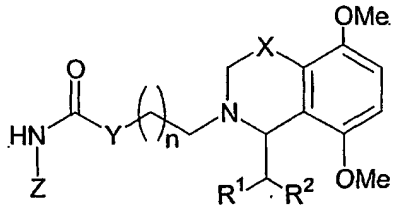


General Formula 10

wherein

R^1, R^2, X, Y, Z, and n have the meaning given in general formula 1 above.

11. Compounds of general formula 11,

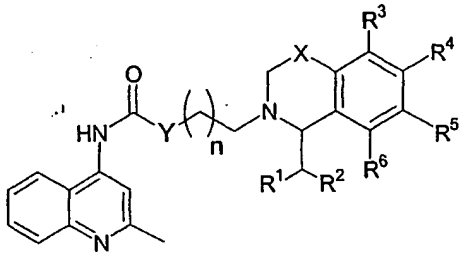


General Formula 11

wherein

R^1, R^2, X, Y, Z, and n have the meaning given in general formula 1 above.

12. Compounds of general formula 12,

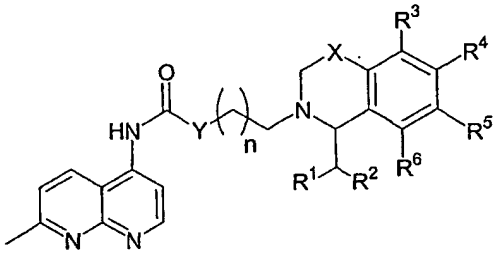


General Formula 12

wherein

R^1, R^2, R^3, R^4, R^5, R^6, X, Y, and n have the meaning given in general formula 1.

13. Compounds of general formula 13,

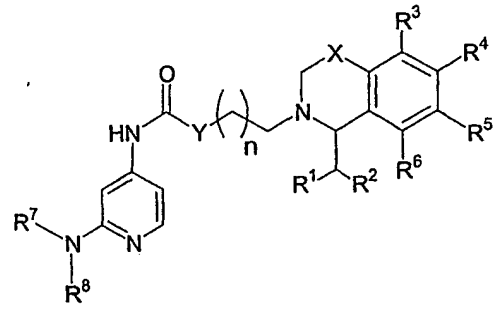


General Formula 13

wherein

R^1, R^2, R^3, R^4, R^5, R^6, X, Y, and n have the meaning given in general formula 1.

14. Compounds of general formula 14,

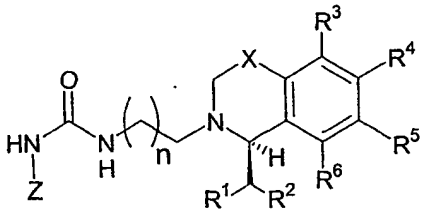


General Formula 14

wherein

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X, Y, and n have the meaning given in general formula 1.

15. Compounds of general formula 15,



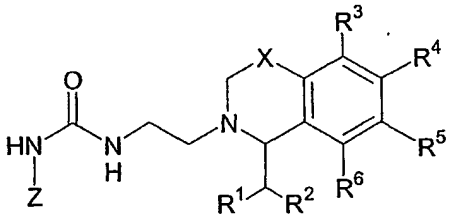
General Formula 15

wherein

the 1 position of the 1,2,3,4-tetrahydroisoquinoline ring system has the R absolute stereochemical configuration;

R^1, R^2, R^3, R^4, R^5, R^6, X, Z, and n have the meaning given in general formula 1.

16. Compounds of general formula 16,



General Formula 16

wherein

R^3, R^4, R^5, and R^6 are independently hydrogen or lower alkyloxy;

R^1, R^2, and Z have the meaning given in general formula 1.

17. The compounds according to any one of claims 1 to 16

1-{2-[1-(4-Fluoro-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[1-(3,4-Difluoro-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[1-(3-Fluoro-4-methoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[1-(3,4-Difluoro-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(3-Fluoro-4-methoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(4-Fluoro-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-(2-{1-[2-(4-Fluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(2,4-Difluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(2,4-Difluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-quinolin-4-yl-urea

1-(2-{1-[2-(3,4-Difluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(3,4-Difluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-quinolin-4-yl-urea

1-(2-{1-[2-(4-Fluoro-phenyl)-ethyl]-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-quinolin-4-yl-urea

1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[(*E*)-2-(2,4-Difluoro-phenyl)-vinyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[(*E*)-2-(2,5-Difluoro-phenyl)-vinyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(2,3-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(2,4-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(2,5-Bis-trifluoromethyl-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(2,5-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(3,4-Difluoro-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(3,4-Dimethoxy-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(3,5-Bis-trifluoromethyl-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{1-[2-(4-Fluoro-phenyl)-ethyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{6,7-Dimethoxy-1-[2-(2-methoxy-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{6,7-Dimethoxy-1-[2-(3-methoxy-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{6,7-Dimethoxy-1-[2-(4-methoxy-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-(2-{6,7-Dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1*H*-isoquinolin-2-yl}-ethyl)-3-(2-methyl-quinolin-4-yl)-urea

1-[2-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea

1-[2-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea

1-[2-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea

1-[3-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-propyl]-3-(2-methyl-quinolin-4-yl)-urea

1-[3-(6,7-Dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-propyl]-3-quinolin-4-yl-urea

1-[2-(1-Benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea

1-[2-(1-Benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea

1-[2-(1-Benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea

1-[2-(1-Benzyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea

1-[2-(1-Benzyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea

1-[2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea

1-[2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea

1-[2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea

1-[2-(1-Benzyl-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea

1-[2-(1-Benzyl-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea

1-[2-(6,7-Dimethoxy-1-naphthalen-2-ylmethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea

1-[2-(6,7-Dimethoxy-1-naphthalen-2-ylmethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea

1-[2-(6,7-Dimethoxy-1-phenoxymethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea

1-[3-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-propyl]-3-(2-methyl-quinolin-4-yl)-urea

1-[3-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-propyl]-3-quinolin-4-yl-urea

1-{2-[1-(2,5-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[1-(2,5-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(2,6-Dichloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[1-(3,4-Difluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[1-(3,4-Difluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(5,6,7,8-tetrahydro-quinolin-4-yl)-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(3-Fluoro-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[1-(3-Fluoro-5-trifluoromethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[1-(4-Chloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[1-(4-Chloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[6,7-Dimethoxy-1-(2,3,4-trimethoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[6,7-Dimethoxy-1-(2,3,4-trimethoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[6,7-Dimethoxy-1-(3,4,5-trimethoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[6,7-Dimethoxy-1-(3,4,5-trimethoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[6,7-Dimethoxy-1-(3,4,5-trimethoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[6,7-Dimethoxy-1-(3-methoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[6,7-Dimethoxy-1-(3-methoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[6,7-Dimethoxy-1-(4-methoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[6,7-Dimethoxy-1-(4-methoxy-benzyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{3-[1-(3,4-Difluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl}-3-quinolin-4-yl-urea

1-{3-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{3-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl}-3-quinolin-4-yl-urea

1-{3-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{3-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl}-3-quinolin-4-yl-urea

1-{3-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl}-3-quinolin-4-yl-urea

1-{2-[5-(3,4-Dimethoxy-benzyl)-7,8-dihydro-5*H*-[1,3]dioxolo[4,5-g]isoquinolin-6-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[5-(3,4-Dimethoxy-benzyl)-7,8-dihydro-5*H*-[1,3]dioxolo[4,5-g]isoquinolin-6-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[6-(3,4-Dimethoxy-benzyl)-2,3,8,9-tetrahydro-6*H*-[1,4]dioxino[2,3-g]isoquinolin-7-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[6-(3,4-Dimethoxy-benzyl)-2,3,8,9-tetrahydro-6*H*-[1,4]dioxino[2,3-g]isoquinolin-7-yl]-ethyl}-3-quinolin-4-yl-urea

1-[2-(1-Benzhydryl-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea

1-[2-(1-Benzhydryl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea

1-[2-(1-Benzhydryl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea

1-[2-(1-Benzyl-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-pyridin-4-yl-urea

1-[2-(1-Benzyl-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-3-quinolin-4-yl-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[6,7-Dimethoxy-1-(1-phenyl-propyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-pyridin-4-yl-urea

1-{2-[6,7-Dimethoxy-1-(1-phenyl-propyl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-4,4-dimethyl-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[(*R*)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[(*R*)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-quinolin-4-yl-urea

1-{2-[(*R*)-1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[7-Benzyloxy-1-(3,4-dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-{2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methyl-quinolin-4-yl)-urea

1-(3,4-Dichloro-benzyl)-6-methoxy-2-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid methylamide

1-(3,4-Dichloro-benzyl)-6-methoxy-2-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid propylamide

1-(3,4-Dichloro-benzyl)-6-methoxy-2-{2-[3-(2-methyl-quinolin-4-yl)-ureido]-ethyl}-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid dimethylamide

1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(7-methyl-[1,8]naphthyridin-4-yl)-urea

1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(5,6,7,8-tetrahydro-quinolin-4-yl)-urea

1-[2-(Benzyl-methyl-amino)-pyridin-4-yl]-3-{2-[1-(4-fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-urea

1-[2-(Benzyl-methyl-amino)-6-methyl-pyridin-4-yl]-3-{2-[1-(4-fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-urea

1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-[2-(methyl-phenyl-amino)-pyridin-4-yl]-urea

1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-pyrrolidin-1-yl-pyridin-4-yl)-urea

1-{2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl}-3-(2-methylamino-1-yl-pyridin-4-yl)-urea

Quinolin-4-yl-carbamic acid 2-(6,7-dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl ester

Quinolin-4-yl-carbamic acid 2-(1-benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl ester

Quinolin-4-yl-carbamic acid 2-[1-(4-fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethyl ester

Quinolin-4-yl-carbamic acid 3-(1-benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-propyl ester

Quinolin-4-yl-carbamic acid 3-(6,7-dimethoxy-1-phenethyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-propyl ester

Quinolin-4-yl-carbamic acid 3-[1-(3,4-difluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl ester

Quinolin-4-yl-carbamic acid 3-[1-(3,4-dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl ester

Quinolin-4-yl-carbamic acid 3-[1-(4-fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-propyl ester

and pharmaceutically acceptable salts thereof.

18. Pharmaceutical compositions containing a compound of any one of claims 1 to 17 and usual carrier materials and adjuvants for the treatment of disorders which are associated with a dysregulation of urotensin II or urotensin II receptors, especially disorders associated with vascular or myocardial dysfunction, such as hypertension, atherosclerosis, angina or myocardial ischemia, congestive heart failure, cardiac insufficiency, cardiac arrhythmias, renal ischemia, chronic kidney disease, renal failure, stroke, cerebral vasospasm, cerebral ischemia, dementia, migraine, subarachnoidal hemorrhage, diabetes, diabetic arteriopathy, asthma, chronic obstructive pulmonary disease, high-altitude pulmonary edema, Raynaud's syndrome, portal hypertension, thyroid dysfunction, pulmonary edema, pulmonary hypertension, or pulmonary fibrosis.

19. Pharmaceutical compositions containing a compound of any one of claims 1 to 17 and usual carrier materials and adjuvants for the treatment of disorders such as prevention of restenosis after balloon or stent angioplasty, cancer, prostatic hypertrophy, erectile dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, gram negative septicemia, shock, sickle cell anemia, glomerulonephritis, renal colic, glaucoma, therapy and prophylaxis of diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, pain, addictions, schizophrenia, Alzheimer's disease, anxiety, obsessive-compulsive behavior, epileptic seizures, stress, depression, dementias, neuromuscular disorders, neurodegenerative diseases.

20. The use of one or more compounds of any one of claims 1 to 17 in combination with other pharmacologically active compounds for the treatment as hypertension, atherosclerosis, angina or myocardial ischemia, congestive heart failure, cardiac insufficiency, cardiac arrhythmias, renal ischemia, chronic kidney disease, renal failure, stroke, cerebral vasospasm, cerebral ischemia, dementia, migraine, subarachnoidal hemorrhage, diabetes, diabetic arteriopathy, asthma, chronic obstructive pulmonary disease, high-altitude

pulmonary edema, Raynaud's syndrome, portal hypertension, thyroid dysfunction, pulmonary edema, pulmonary hypertension, or pulmonary fibrosis, restenosis after balloon or stent angioplasty, cancer, prostatic hypertrophy, erectile dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, gram negative septicemia, shock, sickle cell anemia, glomerulonephritis, renal colic, glaucoma, therapy and prophylaxis of diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, pain, addiction, schizophrenia, Alzheimer's disease, anxiety, obsessive-compulsive behavior, seizures, stress, depression.

21. The use of one or more compounds of any one of claims 1 to 17 in combination with other pharmacologically active compounds such as ACE inhibitors, angiotensin II receptor antagonists, endothelin receptor antagonists, vasopressin antagonists, beta-adrenergic antagonists, alpha-adrenergic antagonists, vasopressin antagonists, TNFalpha antagonists, or peroxisome proliferator activator receptor modulators for the treatment of disorders given in any one of claims 18 to 20.

22. The entire invention as herein before described.

INTERNATIONAL SEARCH REPORT

Inte ɔnal Application No
PCT/EP 02/03131

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/12 A61K31/47 C07D401/12 C07D407/14 C07D471/04
C07D491/04 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 501 693 A (BANYU PHARMA CO LTD) 2 September 1992 (1992-09-02) page 1, line 19 -page 2, line 36	1-21
A,P	WO 01 45694 A (SMITHKLINE BEECHAM CORP ;DHANAK DASHYANT (US); KNIGHT STEVEN D (US) 28 June 2001 (2001-06-28) page 2, line 24 -page 3, line 27	1-21
A,P	WO 01 45711 A (KNIGHT STEVEN DAVID ;SMITHKLINE BEECHAM CORP (US); DHANAK DASHYANT) 28 June 2001 (2001-06-28) page 2, line 20 -page 3, line 22	1-21
A,P	WO 01 45700 A (KNIGHT STEVEN DAVID ;SMITHKLINE BEECHAM CORP (US); WIDDOWSON KATHE) 28 June 2001 (2001-06-28) page 2, line 20 -page 3, line 24	1-21

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 August 2002	16/08/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Usuelli, A

Form PCT/ISA/210 (second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 22

Present claim 22 fails to define the matter for which protection is sought in term of technical features as demanded by Rule 6.3 (a). The scope of this claim is so obscure that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out only in respect to claims 1-21.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/03131

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 20-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 22
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ...nal Application No
PCT/EP 02/03131

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0501693 A	02-09-1992	AT 141918 T	15-09-1996
		AU 644513 B2	09-12-1993
		AU 1121892 A	03-09-1992
		CA 2061260 A1	28-08-1992
		DE 69213049 D1	02-10-1996
		DE 69213049 T2	03-04-1997
		EP 0501693 A1	02-09-1992
		JP 5070436 A	23-03-1993
		US 5362736 A	08-11-1994
WO 0145694 A	28-06-2001	AU 2441801 A	03-07-2001
		WO 0145694 A1	28-06-2001
WO 0145711 A	28-06-2001	WO 0145711 A1	28-06-2001
WO 0145700 A	28-06-2001	WO 0145700 A1	28-06-2001

Form PCT/ISA/210 (patent family annex) (July 1992)

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(74) Agent: **HOFMANN, Dieter**; StratAll, Therwilerstrasse 87, CH-4153 Reinach (CH).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 1,2,3,4-TETRAHYDROISOQUINOLINES DERIVATIVES AS UROTENSIN II RECEPTOR ANTAGONISTS

(57) Abstract: The invention relates to novel 1,2,3,4-tetrahydroisoquinoline derivatives of formula (I) and related compounds and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as neurohormonal antagonists especially urotensin II antagonists.